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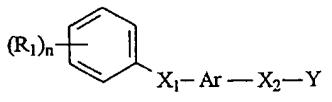
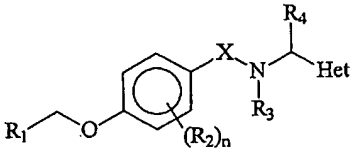


(I)



(II)

(57) Abstract: Compounds of the formulae (I) and (II), and pharmaceutically acceptable salts thereof, are found to be inhibitors of sensory neurone specific (SNS) sodium channels. They are therefore useful as analgesic and neuroprotective agents. Formula (I) & Formula (II) wherein, in the formula (I), R_1 is an organic substituent, X_1 and X_2 are direct bonds or spacer moieties, Ar is aryl or heteroaryl and Y is a substituted aminoalkyl group or a heteroaryl-, heterocyclyl- or phenyl-containing moiety and, in the formula(II), R_1, R_2, R_3, Ar and R_4 are organic substituents, X is a spacer moiety and Het is a 5-membered heteroaryl or heterocyclyl group.

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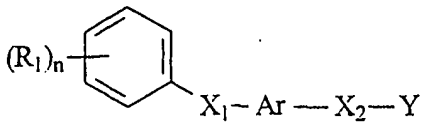
CHEMICAL COMPOUNDS

The present invention relates to a series of inhibitors of the subtype of mammalian sodium channels known as $Na_v1.8$ or sensory neurone specific (SNS) channels. The $Na_v1.8$ channel is a 1,957 amino acid tetrodotoxin-insensitive voltage-gated sodium channel. The sodium channel, nucleic acid sequences coding for the channel, vectors, host cells and methods of identifying modulators, are taught in US-A-6451554. The α-subunit gene corresponding to this ion channel is referred to as SCN10A. The channel is described in more detail in Akopian *et al.*, (1996), 379, 257-262.

Mammalian ion channels are becoming increasingly well characterized, and progress in sodium channel research has been summarized recently in Anger *et al*, J. Med. Chem. (2001) 44, 115-137. Sodium channels are recognised as valid targets for pain therapeutics, and blockade of sodium channels can be useful in the treatment of a range of pain syndromes (see for example Black *et al*, Progress in Pain Research and Management (2001), 21(Neuropathic Pain: Pathophysiology and Treatment), 19-36).

It has now surprisingly been found that compounds of the general formulae (I) and (II) set out below act as inhibitors of sensory neurone specific sodium channels.

The present invention therefore provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment or prevention of a condition where SNS sodium channels are involved in the underlying mechanism of the disease or in producing symptoms that can be treated separately



(I)

wherein:

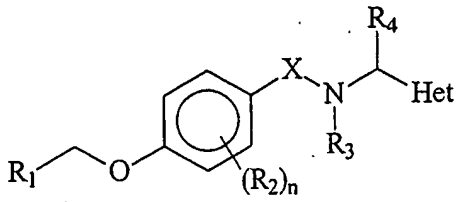
- each R_1 is the same or different and represents halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, hydroxy, amino, C_1-C_6 alkylamino or di-(C_1-C_6 alkyl)amino;
- n is 0, 1, 2 or 3;
- X_1 represents a direct bond, -L-O-L'-, -L-S-L'- or -L-NR'-L'- wherein L and L' are the same or different and each represent a direct bond or C_1-C_4 alkylene group and R' represents hydrogen or C_1-C_4 alkyl;
- Ar represents a 5- to 6- membered heteroaryl group or a phenyl group which is optionally fused to a 5- membered heteroaryl group;
- X_2 represents a direct bond, -L''-O-, -L''-S-, L''-NR'-, -CO-, -CO_2-, -S(O)-, -$S(O)_2$-, -CO-NR'-, -S(O)-NR'- or -$S(O)_2$-NR'-, wherein L'' represents a direct bond or C_1-C_4 alkylene group and R' represents hydrogen or C_1-C_4 alkyl; and
- Y represents -L'''-NR'R'' or a -(C_1-C_6 alkyl)-(5- to 10- membered heteroaryl), -(C_1-C_6 alkyl)-(5- to 10- membered heterocyclyl), -(C_1-C_6 alkyl)-phenyl, phenyl, 5- to 10- membered heteroaryl or 5- to 10- membered heterocyclyl group, wherein L''' is a C_1-C_4 alkylene group and R' and R'' are the same or different and each represent hydrogen, C_1-C_6 alkyl or phenyl, provided that (a) when Y is a 5- to 10- membered heteroaryl group it is other than a pyridyl group and (b) when X_1 is -O-, -S- or -NR'-, X_2 is a direct bond and Y is a 5- to 10- membered heteroaryl group which contains 1 or 2 heteroatoms selected from N, O and S, the 5- to 10- membered heteroaryl group is attached via a carbon atom which is not adjacent to a N atom,

wherein:

- the alkyl and alkylene groups and moieties in the substituents R_1, X_1, X_2 and Y are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylamino and di(C_1-C_4 alkyl)amino substituents; and
- the phenyl, heteroaryl and heterocyclyl groups in the substituents Ar_1 and Y are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, hydroxy, -NR'R'', C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6

haloalkylthio, cyano, nitro, $-CONR'R''$, $-S(O)_2-NR'R''$, $-CO_2-R''$, $-S(O)_2R''$ and phenyl substituents, wherein R' and R'' are the same or different and each represent hydrogen or C_1-C_4 alkyl.

Also provided is the use of a compound of the formula (II), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment or preparation of a condition where SNS sodium channels are involved in the underlying mechanism of the disease or in producing symptoms that can be treated separately



(II)

wherein:

- R_1 represents hydrogen, C_1-C_6 alkyl, C_6-C_{10} aryl, a 5- to 10- membered heteroaryl group, a 5- to 10- membered heterocyclyl group or a C_3-C_6 carbocyclyl group;
- each R_2 is the same or different and represents C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy, C_1-C_6 alkythio, hydroxy, nitro, cyano, amino, (C_1-C_6 alkyl)amino or di-(C_1-C_6 alkyl)amino;
- R_3 represents hydrogen, C_1-C_6 alkyl, or together with R_4 represents a C_2-C_4 alkylene group;
- R_4 represents hydrogen, C_1-C_6 alkyl, C_6-C_{10} aryl, C_3-C_6 carbocyclyl, a 5- to 10- membered heteroaryl group, a 5- to 10- membered heterocyclyl group, -(C_1-C_6 alkyl)-aryl, -(C_1-C_6 alkyl)-(C_3-C_6 carbocyclyl), -(C_1-C_6 alkyl)-(5- to 10- membered heteroaryl), -(C_1-C_6 alkyl)-(5- to 10- membered heterocyclyl) or, together with R_3 represents a C_2-C_4 alkylene group;
- n is 0, 1, 2, 3 or 4;
- X represents a $-CH_2-$, -CO-, -SO- or $-S(O)_2-$ group; and
- Het represents a 5- membered heteroaryl group or a 5- membered heterocyclyl group;

wherein:

- the alkyl and alkylene groups and moieties in the substituents R_1 to R_4 are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylamino and di(C_1-C_4 alkyl)amino substituents; and
- the aryl, heteroaryl, heterocyclyl and carbocyclyl groups and moieties in the substituents R_1, R_4 and Het are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, hydroxy, nitro, cyano, amino, C_1-C_6 alkylamino, di-(C_1-C_6 alkyl)amino, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy and C_1-C_6 haloalkylthio substituents.

As used herein, a C_1-C_6 alkyl group or moiety is a linear or branched alkyl group or moiety containing from 1 to 6 carbon atoms, such as a C_1-C_5 alkyl group or C_1-C_4 alkyl group or moiety, for example methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, $-CHEt_2$ and $-CH_2CHMe_2$.

As used herein, a C_1-C_4 alkylene group or a C_2-C_4 alkylene group is a linear or branched alkylene group. Typically, it is a methylene, ethylene, propylene, butylene (e.g. n-butylene) or –CH(Me)- group. Preferably it is a propylene group.

As used herein, a C_6-C_{10} aryl group or moiety is typically a phenyl or naphthyl group or moiety. Preferably, it is a phenyl moiety.

As used herein, a 5- to 10- membered heteroaryl group or moiety is a 5- to 10- membered aromatic ring, such as a 5- or 6- membered ring, containing at least one heteroatom, for example 1, 2 or 3 heteroatoms, selected from O, S and N. Examples include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, imidazolyl, triazolyl, pyrazolidinyl, pyrrolyl, oxadiazolyl, oxazolyl, isoxazolyl, thiadiazolyl, thiazolyl and pyrazolyl groups. Preferred heteroaryl groups and moieties in the formula (I) are 5- membered rings, for example triazolyl, imidazolyl, thiazolyl, thiadiazolyl, pyrazolyl and furanyl groups and moieties. In the formula (II), thienyl, thiazolyl, oxazolyl, imidazolyl, pyrrolyl, pyrazolyl, isoxazolyl and furanyl groups are preferred.

As used herein, a halogen is typically chlorine, fluorine, bromine or iodine and is preferably chlorine or fluorine. As used herein, a said C_1-C_6 alkoxy group is typically a said C_1-C_6 alkyl group attached to an oxygen atom. A said C_1-C_6 alkylthio group is typically a said C_1-C_6 alkyl group attached to a thio group.

As used herein, a C_1-C_6 haloalkyl group is typically a said C_1-C_6 alkyl group, for example a C_1-C_4 alkyl group, substituted by one or more said halogen atoms. Typically, it is substituted by 1, 2 or 3 said halogen atoms. Preferred haloalkyl groups include perhaloalkyl groups such as $-CX_3$ wherein X is a said halogen atom. Particularly preferred haloalkyl groups are $-CF_3$ and $-CCl_3$.

As used herein, a C_1-C_6 haloalkoxy group is typically a said C_1-C_6 alkoxy group, for example a C_1-C_4 alkoxy group, substituted by one or more said halogen atoms. Typically, it is substituted by 1, 2 or 3 said halogen atoms. Preferred haloalkoxy groups include perhaloalkoxy groups such as $-OCX_3$ wherein X is a said halogen atom. Particularly preferred haloalkoxy groups are $-OCF_3$ and $-OCCl_3$.

As used herein, a C_1-C_6 haloalkylthio group is typically a said C_1-C_6 alkylthio group, for example a C_1-C_4 alkylthio group, substituted by one or more said halogen atoms. Typically, it is substituted by 1, 2 or 3 said halogen atoms. Preferred haloalkylthio groups include perhaloalkylthio groups such as $-SCX_3$ wherein X is a said halogen atom. Particularly preferred haloalkylthio groups are $-SCF_3$ and $-SCCl_3$.

As used herein, a C_3-C_6 carbocyclyl group or moiety is a non-aromatic saturated or unsaturated hydrocarbon ring, having from 3 to 6 carbon atoms. Preferably it is a saturated group, i.e. a C_3-C_6 cycloalkyl group. Examples include cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, a 5- to 10- membered heterocyclyl group or moiety is a non-aromatic, saturated or unsaturated C_5-C_{10} carbocyclic ring, for example a 5- or 6-membered ring, in which one or more, for example 1, 2 or 3, of the carbon atoms are replaced by a heteroatom selected from N, O and S. Saturated heterocyclyl groups are preferred. Examples of suitable heterocyclyl groups include piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, imidazolidinyl, thiazolidinyl, 1,4 dioxanyl and 1,3 dioxolanyl. Piperidyl and morpholinyl groups are preferred.

For the avoidance of doubt, the orientation of the X_1 moiety in the formula (I) is such that the right hand side of the depicted moieties is attached to the group Ar. Similarly, for the avoidance of doubt, the orientation of the X_2 moiety in the formula (I) is such that the right hand side of the depicted moieties is attached to the group Y. When X_2 is $-CO_2-$ it can represent either a -CO-O- or an -O-CO- moiety.

Typically, the alkyl and alkylene groups and moieties in the substituents R_1, X_1, X_2 and Y in the formula (I) are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_2 alkoxy, C_1-C_2 alkylthio, C_1-C_2 alkylamino and di(C_1-C_2 alkyl)amino substituents. Preferably, the alkyl and alkylene groups and moieties in the substituents R_1, X_1, X_2 and Y in the formula (I) are unsubstituted or are substituted by 1 or 2 substituents selected from halogen, hydroxy, C_1-C_2 alkoxy and C_1-C_2 alkylthio substituents. More preferably, the alkyl and alkylene groups and moieties in the substituents R_1, X_1, X_2 and Y in the formula (I) are unsubstituted.

Typically, when a said phenyl, heteroaryl or heterocyclyl group or moiety in the formula (I) carries a nitro, cyano, $-CONR'R''$, $-S(O)_2-NR'R''$, $-CO_2R''$, $-S(O)_2R''$ or phenyl substituent, only one of the substituents on the phenyl, heteroaryl or heterocyclyl group or moiety is a nitro, cyano, $-CONR'R''$, $-S(O)_2NR'R''$, $-CO_2R''$, $-S(O)_2R''$ or phenyl group. Further, the phenyl, heteroaryl and heterocyclyl groups and moieties in the substituents Ar and Y in the formula (I) are typically unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, hydroxy, $-NR'R''$, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 haloalkylthio, $-CONR'R''$ and phenyl substituents, wherein R' and R'' are the same or different and each represent hydrogen or C_1-C_4 alkyl. Preferably, the phenyl, heteroaryl and heterocyclyl groups and moieties in the substituents Ar and Y in the formula (I) are unsubstituted or are substituted by 1 or 2 substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_2 alkyl, C_1-C_2 alkoxy, C_1-C_2 alkylthio, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_2 haloalkylthio, carbamyl and phenyl substituents.

For the avoidance of doubt, the substituents on said alkyl, alkylene, phenyl, heteroaryl and heterocyclyl groups and moieties are themselves unsubstituted.

Typically, each R_1 in the formula (I) is the same or different and represents halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or C_1-C_4 alkylthio. Preferably, each R_1 in the formula (I) is the same or different and represents halogen or an unsubstituted C_1-C_2 alkyl, C_1-C_2 haloalkyl, C_1-C_2 alkoxy, C_1-C_2 haloalkoxy, C_1-C_2 alkylthio or C_1-C_2

haloalkylthio group. More preferably, each R_1 in the formula (I) is the same or different and is a halogen atom.

Typically, n in the formula (I) is 0, 1 or 2.

Typically, each L and L′ moiety in the X_1 group in the formula (I) is a direct bond or a methylene or ethylene group. Preferably, each L and L′ moiety in the formula (I) is unsubstituted.

In a preferred embodiment of the invention, X_1 in the formula (I) is -O- or -S-. In a further preferred embodiment of the invention, X_1 in the formula (I) is -L-O- or -L-S- wherein L is a C_1-C_4 alkylene group. In a further preferred embodiment of the invention, X_1 in the formula (I) is a direct bond.

Preferably, X_1 in the formula (I) is unsubstituted. Most preferably, X_1 in the formula (I) is a direct bond, $-CH_2-O-$ or -O-. Further, X_1 in the formula (I) is typically not a direct bond when X_2 is a direct bond.

Typically, Ar in the formula (I) is a 5- membered heteroaryl group, a phenyl group or a phenyl group fused to a 5- membered heteroaryl group. Preferably, Ar in the formula (I) is a triazolyl, imidazolyl, phenyl, benzofuranyl, benzothienyl or indolyl group. More preferably, Ar in the formula (I) is phenyl, triazolyl or benzofuranyl.

Typically, the Ar group in the formula (I) is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, hydroxy, C_1-C_2 alkyl, C_1-C_2 haloalkyl, C_1-C_2 alkoxy, C_1-C_2 haloalkoxy, C_1-C_2 alkylthio and C_1-C_2 haloalkylthio substituents. Preferably, the Ar group in the formula (I) is unsubstituted or substituted by a halogen, C_1-C_2 alkyl or C_1-C_2 alkoxy substituent.

Typically, each L″ moiety in the X_2 group in the formula (I) is a methylene or ethylene group. Preferably, each L″ moiety in the formula (I) is unsubstituted.

Typically, X_2 in the formula (I) represents a direct bond, -L″-NR′-, -CO-, -S(O)-, $-S(O)_2-$, -CO-NR′- or $-S(O)_2-NR'-$ wherein L″ is as defined above and R′ is hydrogen, methyl or ethyl.

Preferably, X_2 in the formula (I) is unsubstituted. More preferably, X_2 in the formula (I) is a direct bond, $-CH_2-NH-$, $-S(O)_2-NH-$ or $-S(O)_2-$. Further, X_2 in the

formula (I) is typically not a direct bond when X_1 is a direct bond. Preferably, X_2 in the formula (I) is not a direct bond when X_1 is -O-, -S-, -NR'- or a direct bond.

Typically, L''' in the Y substituent in the formula (I) is an unsubstituted C_1-C_4 alkylene group.

Preferably, Y in the formula (I) represents -(C_1-C_4 alkyl)-N(C_1-C_4 alkyl)$_2$, or a -(C_1-C_4 alkyl)-(5- to 10- membered heteroaryl), -(C_1-C_4 alkyl)-(5- to 10- membered heterocyclyl), -(C_1-C_4 alkyl)-phenyl, phenyl, 5- membered heteroaryl or 5- to 10- membered heterocyclyl group, provided that when X_1 is -O-, -S- or -NR'-, X_2 is a direct bond and Y is a heteroaryl group which contains 1 or 2 heteroatoms selected from N, O or S, Y is attached via a carbon atom which is not adjacent to a N atom. More typically, whenever Y in the formula (I) is a 5- membered heteroaryl group, either X_1 is -O-CH_2- or X_2 is other than a direct bond.

Preferably, the phenyl, heteroaryl and heterocyclyl groups and moieties in the Y substituent in the formula (I) are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, amino, C_1-C_2 alkyl, C_1-C_2 alkoxy, C_1-C_2 alkylthio, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_2 haloalkylthio, carbamyl and phenyl substituents.

In one embodiment of the invention, Y is other than a phenyl substituted thiazolyl group. More typically, in this embodiment, the Y substituent is not substituted by a phenyl group.

Preferred compounds of formula (I) are those in which:

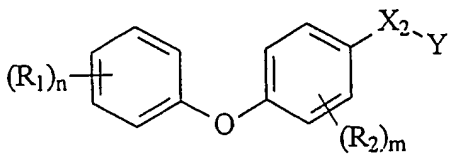
- each R_1 is the same or different and represents halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or C_1-C_4 alkylthio;
- n is 0, 1 or 2;
- X_1 represents a direct bond, -O-, -S-, -L-O- or -L-S- wherein L is a C_1-C_4 alkylene group;
- Ar represents a 5- membered heteroaryl group, a phenyl group or a phenyl group fused to a 5- membered heteroaryl group;
- X_2 represents a direct bond, -L''-NR'-, -CO-, -S(O)-, -S(O)$_2$-, -CO-NR'- or -S(O)$_2$-NR'- wherein L'' is a methylene or ethylene group and R' is hydrogen, methyl or ethyl, provided that X_2 is not a direct bond when X_1 is a direct bond;

- Y represents -(C_1-C_4 alkyl)-N(C_1-C_4 alkyl)$_2$, or a -(C_1-C_4 alkyl)-(5- to 10-membered heteroaryl), -(C_1-C_4 alkyl)-(5- to 10- membered heterocyclyl), -(C_1-C_4 alkyl)-phenyl, phenyl, 5- membered heteroaryl or 5- to 10- membered heterocyclyl group, provided that when X_1 is -O-, -S- or -NR'-, X_2 is a direct bond and Y is a heteroaryl group which contains 1 or 2 heteroatoms selected from N, O or S, Y is attached via a carbon atom which is not adjacent to a N atom,

wherein:

- the alkylene groups and moieties in the substituents X_1 and X_2 are unsubstituted and the alkyl groups and moieties in the substituents R_1 and Y are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_2 alkoxy, C_1-C_2 alkylthio, C_1-C_2 alkylamino and di(C_1-C_2 alkyl)amino substituents; and
- the phenyl, heteroaryl and heterocyclyl groups and moieties in the substituents Ar and Y are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, hydroxy, -NR'R'', C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 haloalkylthio, -CONR'R'' and phenyl substituents, wherein R' and R'' are the same or different and each represent hydrogen or C_1-C_4 alkyl, provided that when a phenyl, heteroaryl or heterocyclyl group or moiety carries a -CONR'R'' or phenyl substituent, only one of the substituents on the phenyl, heteroaryl or heterocyclyl group or moiety is a -CONR'R'' or phenyl substituent.

Particularly preferred compounds of the formula (I) are compounds of formula (Ia),



(Ia)

wherein:

- each R_1 is the same or different and is as defined above;
- n is as defined above;
- each R_2 is the same or different and is halogen, hydroxy, C_1-C_2 alkyl, C_1-C_2 haloalkyl, C_1-C_2 alkoxy, C_1-C_2 haloalkoxy, C_1-C_2 alkylthio or C_1-C_2 haloalkylthio;
- m is 0, 1 or 2;
- X_2 is as defined above; and
- Y is -(C_1-C_4 alkyl)-N(C_1-C_4 alkyl)$_2$ or a -(C_1-C_4 alkyl)-(5- to 6- membered heteroaryl), -(C_1-C_4 alkyl)-(5- to 10- membered heterocyclyl), 5- membered heteroaryl or 5- to 10- membered heterocyclyl group, provided that when X_2 is a direct bond and Y is a heteroaryl group containing 1 or 2 heteroatoms selected from N, O and S, Y is attached via a carbon atom which is not adjacent to a nitrogen atom,

wherein:

- the alkyl and alkylene groups and moieties in the substituents R_1, R_2, X_2 and Y are unsubstituted; and
- the heteroaryl and heterocyclyl groups and moieties in the substituent Y are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_2 alkyl, C_1-C_2 alkoxy, C_1-C_2 alkylthio, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_2 haloalkylthio, carbamyl and phenyl substituents.

Preferably, each R_1 in the formula (Ia) is other than an amino group. More preferably, each R_1 in the formula (Ia) is the same or different and is a halogen atom. Preferably, n in the formula (Ia) is 0, 1 or 2. Preferably, X_2 in the formula (Ia) is -CH_2-NH-, -$S(O)_2$-NH- or -$S(O)_2$-.

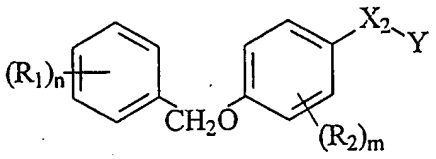
Preferably, each R_2 in the formula (Ia) is the same or different and is C_1-C_2 alkyl or C_1-C_2 alkoxy. Preferably, m in the formula (Ia) is 0 or 1.

Preferably, Y in the formula (Ia) is -(C_1-C_2 alkyl)-N(C_1-C_2 alkyl)$_2$ or a -(C_1-C_2 alkyl)-(5- to 6- membered heteroaryl), -(C_1-C_2 alkyl)-(5- to 6- membered heterocyclyl), 5- membered heteroaryl or 5- to 6- membered heterocyclyl group, provided that when X_2 is a direct bond and Y is a heteroaryl group containing 1 or 2 heteroatoms selected from N, O and S, Y is attached via a carbon atom which is not adjacent to a nitrogen atom.

More preferably, Y in the formula (Ia) is -(C_1-C_2 alkyl)-N(C_1-C_2 alkyl)$_2$ or a triazolyl, pyrazolyl, thiazolyl, thiadiazolyl, piperidyl, -methyl-piperidyl or -methyl-triazolyl group, the triazolyl, pyrazolyl, thiazolyl, thiadiazolyl and piperidyl groups and moieties being unsubstituted or substituted by an amino, C_1-C_2 alkyl, C_1-C_2 alkoxy, C_1-C_2 alkylthio, carbamyl or phenyl substituent, provided that when Y is a pyrazolyl or thiazolyl group it is attached via a carbon atom which is not adjacent to a nitrogen atom.

In one embodiment, Y in the formula (Ia) is not a phenyl substituted thiazolyl group.

Further preferred compounds of the formula (I) are compounds of formula (Ib),



(Ib)

wherein:

- R_1, R_2, n, m and X_2 are as defined in the formula (Ia); and
- Y is -(C_1-C_4 alkyl)-N(C_1-C_4 alkyl)$_2$ or a -(C_1-C_4 alkyl)-(5- to 6- membered heteroaryl), -(C_1-C_4 alkyl)-(5- to 10- membered heterocyclyl), 5- membered heteroaryl or 5- to 10- membered heterocyclyl group,

wherein:

- the alkyl and alkylene groups and moieties in the substituents R_1, R_2, X_2 and Y are unsubstituted; and
- the heteroaryl and heterocyclyl groups and moieties in the substituent Y are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_2 alkyl, C_1-C_2 alkoxy, C_1-C_2 alkylthio, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_2 haloalkylthio, carbamyl and phenyl substituents.

Preferably, each R_1 in the formula (Ib) is other than an amino group. More preferably, each R_1 in the formula (Ib) is the same or different and is a halogen atom.

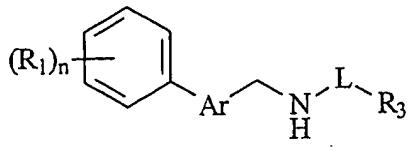
Preferably, n in the formula (Ib) is 0, 1 or 2. Preferably, X_2 in the formula (Ib) is $-CH_2-NH-$, $-S(O)_2-NH-$ or $-S(O)_2-$.

Preferably, each R_2 in the formula (Ib) is the same or different and is C_1-C_2 alkyl or C_1-C_2 alkoxy. Preferably, m in the formula (Ib) is 0 or 1.

Preferably, Y in the formula (Ib) is -(C_1-C_2 alkyl)-N(C_1-C_2 alkyl)$_2$ or a -(C_1-C_2 alkyl)-(5- to 6- membered heteroaryl), -(C_1-C_2 alkyl)-(5- to 6- membered heterocyclyl), 5- membered heteroaryl or 5- to 6- membered heterocyclyl group. More preferably, Y in the formula (Ib) is -(C_1-C_2 alkyl)-N(C_1-C_2 alkyl)$_2$ or a triazolyl, pyrazolyl, thiazolyl, thiadiazolyl, piperidyl, -methyl-piperidyl or -methyl-triazolyl group, the triazolyl, pyrazolyl, thiazolyl, thiadiazolyl and piperidyl groups and moieties being unsubstituted or substituted by an amino, C_1-C_2 alkyl, C_1-C_2 alkoxy, C_1-C_2 alkylthio, carbamyl or phenyl substituent.

In one embodiment, Y in the formula (Ib) is not a phenyl substituted thiazolyl group.

Further preferred compounds of the formula (I) are compounds of formula (Ic) and pharmaceutically acceptable salts thereof



(Ic)

wherein:

- each R_1 is the same or different and is as defined above;
- n is as defined above;
- Ar is as defined above;
- L is a C_1-C_4 alkylene group; and
- R_3 is phenyl, 5- to 6- membered heteroaryl or 5- to 6- membered heterocyclyl,

wherein:

- the alkyl and alkylene groups and moieties in the substituents R_1 and L are unsubstituted; and
- the phenyl, heteroaryl and heterocyclyl groups and moieties in the substituents Ar and R_3 are unsubstituted or are substituted by one or two substituents selected from halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, C_1-C_2 alkylthio, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy and C_1-C_2 haloalkylthio substituents.

Preferably, each R_1 in the formula (Ic) is the same or different and is a halogen atom. Preferably, n in the formula (Ic) is 0. Preferably, L in the formula (Ic) is n-butyl or -CH(CH_3)-.

Preferably, Ar in the formula (Ic) is an unsubstituted triazolyl, imidazolyl, phenyl, benzofuranyl, benzothienyl or indolyl group. More preferably, Ar in the formula (Ic) is an unsubstituted triazolyl or benzofuranyl group.

Preferably, R_3 in the formula (Ic) is a phenyl or 5- membered heteroaryl group which is unsubstituted or substituted by a C_1-C_2 alkyl substituent. More preferably, R_3 is a phenyl or thiazolyl group which is unsubstituted or substituted by a C_1-C_2 alkyl group.

Examples of the particularly preferred compounds of formulae (Ia), (Ib) and (Ic) are:

N*3*-(4-phenoxy-benzyl)-1H-[1,2,4]triazole-3,5-diamine

(4-phenyl-butyl)-(5-phenyl-2H-[1,2,3]triazol-4-ylmethyl)-amine

4-(4-fluoro-phenoxy)-N-(4-methyl-thiazol-2-yl)-benzenesulfonamide

4-(4-fluoro-phenoxy)-N-(2-piperidin-1-yl-ethyl)-benzenesulfonamide

4-(4-fluoro-phenoxy)-N-(5-methylsulfanyl-[1,3,4]thiadiazol-2-yl)-benzenesulfonamide

1-[4-(4-fluoro-phenoxy)-benzenesulfonyl]-piperidine-3-carboxylic acid amide

(4-phenoxy-benzyl)-(5-phenyl-2H-[1,2,3]triazol-4-ylmethyl)-amine

N-(2-diethylamino-ethyl)-4-(4-fluoro-phenoxy)-benzenesulfonamide

4-[4-(2,6-difluoro-benzyloxy)-phenyl]-1H-pyrazole

3-[4-(2,6-difluoro-benzyloxy)-3-methoxy-phenyl]-pyrazole-1-carboxylic acid amide

3-[4-(2,6-difluoro-benzyloxy)-phenyl]-pyrazole-1-carboxylic acid amide

3-[4-(2,6-difluoro-benzyloxy)-3-methoxy-phenyl]-1H-pyrazole

[4-(2-chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-(2-morpholin-4-yl-ethyl)-amine

[4-(2,6-difluoro-benzyloxy)-3-methoxy-benzyl]-(2-morpholin-4-yl-ethyl)-amine

(S)-[1-(5-methyl-thiazol-2-yl)-ethyl]-(2-phenyl-benzofuran-5-yl-methyl)-amine

and pharmaceutically acceptable salts thereof.

Typically, the alkyl and alkylene groups and moieties in the substituents R_1 to R_4 in the formula (II) are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-

C_2 alkoxy, C_1-C_2 alkylthio, C_1-C_2 alkylamino and di(C_1-C_2 alkyl)amino substituents. Preferably, the alkyl and alkylene groups and moieties in the substituents R_1 to R_4 in the formula (II) are unsubstituted or are substituted by 1 or 2 substituents selected from hydroxy, C_1-C_2 alkoxy and C_1-C_2 alkylthio substituents. More preferably, the alkyl and alkylene groups and moieties in the substituents R_1 to R_4 in the formula (II) are unsubstituted.

Typically, when a said aryl, heteroaryl, heterocyclyl or carbocyclyl group or moiety in the formula (II) carries a nitro or cyano substituent, only one of the substituents on the aryl, heteroaryl, heterocyclyl, or carbocyclyl group is a nitro or cyano group. Further, the aryl, heteroaryl, heterocyclyl and carbocyclyl groups and moieties in the substituents R_1, R_4 and Het in the formula (II) are typically unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, hydroxy, cyano, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy and C_1-C_4 haloalkylthio substituents. Preferably, the aryl, heteroaryl, heterocyclyl and carbocyclyl groups and moieties in the substituents R_1, R_4 and Het in the formula (II) are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, hydroxy, cyano, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy and C_1-C_2 haloalkylthio substituents.

For the avoidance of doubt, the substituents on said alkyl, alkylene, aryl, heteroaryl, heterocyclyl and carbocyclyl groups and moieties are themselves unsubstituted.

Typically, R_1 in the formula (II) is hydrogen, C_1-C_6 alkyl, C_6-C_{10} aryl, a 5- to 10- membered heteroaryl group or a C_3-C_6 cycloalkyl group.

Preferably, R_1 in the formula (II) is hydrogen, an unsubstituted C_1-C_6 alkyl group, an unsubstituted C_3-C_6 cycloalkyl group or a C_6 to C_{10} aryl or 5- to 10-membered heteroaryl group, which aryl or heteroaryl group is unsubstituted or substituted with 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, hydroxy, nitro, cyano, amino, C_1-C_6 alkylamino, di-(C_1-C_6 alkyl)amino, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy and C_1-C_6 haloalkylthio substituents. More preferably, R_1 in the formula (II) is hydrogen, an unsubstituted C_1-C_6 alkyl group, an unsubstituted C_3-C_6 cycloalkyl group or a phenyl group which is unsubstituted or substituted by 1, 2 or 3

substituents, preferably 1 or 2 substituents, selected from halogen, cyano, C_1-C_2 alkyl, C_1-C_2 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy and C_1-C_2 haloalkylthio substituents.

Most preferably, R_1 in the formula (II) is hydrogen, an unsubstituted C_1-C_4 alkyl group, an unsubstituted cyclohexyl group or a phenyl group which is unsubstituted or substituted by 1, 2 or 3 substituents, preferably 1 or 2 substituents, selected from halogen, cyano, C_1-C_2 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy and C_1-C_2 haloalkylthio substituents.

Typically, when n in the formula (II) is more than 1, not more than one R_2 substituent represents a group selected from nitro and cyano. Thus, when the central phenyl ring carries a nitro or cyano substituent, typically only one of the substituents on the phenyl ring is a nitro or cyano group.

Typically, each R_2 substituent in the formula (II) is the same or different and represents C_1-C_4 alkyl, halogen, C_1-C_4 alkoxy, C_1-C_4 alkylthio, hydroxy, nitro, cyano, amino, (C_1-C_4 alkyl)amino or di(C_1-C_4 alkyl)amino. Preferably, the or each R_2 substituent in the formula (II) is unsubstituted.

More preferably, each R_2 substituent in the formula (II) is the same or different and represents halogen, hydroxyl, amino, nitro or an unsubstituted C_1-C_2 alkyl, C_1-C_2 alkoxy, (C_1-C_2 alkyl)amino or di(C_1-C_2 alkyl)amino group. Most preferably, each R_2 substituent in the formula (II) is the same or different and represents halogen, nitro, or an unsubstituted C_1-C_2 alkyl or C_1-C_2 alkoxy group.

Preferably, n in the formula (II) is 0, 1 or 2.

Typically, X in the formula (II) represents -CO-, -SO_2- or -CH_2-. Preferably, X in the formula (II) represents -CH_2-.

Typically, R_3 in the formula (II) represents hydrogen or C_1-C_4 alkyl or, together with R_4, represents an unsubstituted C_2-C_4 alkylene group. Preferably, the R_3 substituent in the formula (II) is unsubstituted. More preferably, R_3 in the formula (II) is hydrogen.

Typically, R_4 in the formula (II) represents hydrogen, C_1-C_6 alkyl, C_6-C_{10} aryl, C_3-C_6 carbocyclyl, a 5- to 10- membered heteroaryl group, a 5- to 10- membered heterocyclyl group, -(C_1-C_2 alkyl)-(C_6-C_{10} aryl), -(C_1-C_2 alkyl)-(C_3-C_6 carbocyclyl), -(C_1-C_2 alkyl)-(5- to 10- membered heteroaryl), -(C_1-C_2 alkyl)-(5- to 10- membered heterocyclyl) or, together with R_3, represents a C_2-C_4 alkylene group.

Preferably, R_4 in the formula (II) represents hydrogen, C_1-C_4 alkyl, phenyl, C_3-C_6 cycloalkyl, a 5- or 6- membered heteroaryl group, -(C_1-C_2 alkyl)-phenyl or, together with R_3, represents an unsubstituted C_2-C_4 alkylene group.

Preferably, the R_4 substituent in the formula (II) is unsubstituted or substituted with 1 or 2 substituents selected from hydroxy, methoxy and methylthio substituents. More preferably, the R_4 substituent in the formula (II) is unsubstituted.

Most preferably, R_4 in the formula (II) is hydrogen or an unsubstituted C_1-C_4 alkyl, phenyl or benzyl group.

Typically, Het in the formula (II) represents a 5- membered heteroaryl group containing 1 or 2 heteroatoms selected from N, O and S.

Typically, the Het moiety in the formula (II) is unsubstituted or is substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy and C_1-C_4 haloalkylthio substituents. Preferably, the Het moiety in the formula (II) is unsubstituted or is substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_2 alkyl and C_1-C_2 haloalkyl substituents. More preferably, the Het moiety in the formula (II) is unsubstituted or is substituted by 1, 2 or 3 substituents which are the same or different and are selected from methyl and ethyl substituents.

Most preferably, Het in the formula (II) represents a thiazolyl, oxazolyl, imidazolyl, pyrrolyl, thienyl, pyrazolyl, furanyl or isoxazolyl moiety which is unsubstituted or substituted by 1, 2 or 3 methyl or ethyl substituents.

In one embodiment, Het in the formula (II) is other than furanyl.

Preferred compounds of formula (II) are those in which:

- R_1 is hydrogen, C_1-C_6 alkyl, C_6-C_{10} aryl, a 5- to 10- membered heteroaryl group or a C_3-C_6 cycloalkyl group;
- n is 1, 2, 3 or 4;
- each R_2 is the same or different and represents C_1-C_4 alkyl, halogen, C_1-C_4 alkoxy, C_1-C_4 alkylthio, hydroxy, nitro, cyano, amino, (C_1-C_4 alkyl)amino or di(C_1-C_4 alkyl)amino, provided that not more than one R_2 substituent represents a group selected from nitro or cyano;
- X represents -CH_2-, -CO- or -$S(O)_2$-;
- R_3 represents hydrogen or C_1-C_4 alkyl or, together with R_4, represents

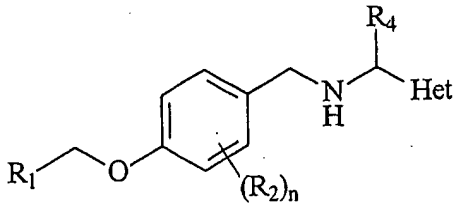
$-(CH_2)_r-$ wherein r is from 2 to 4;

- R_4 represents hydrogen, C_1-C_6 alkyl, C_6-C_{10} aryl, C_3-C_6 carbocyclyl, a 5- to 10- membered heteroaryl group, a 5- to 10- membered heterocyclyl group, -(C_1-C_2 alkyl)-(C_6-C_{10} aryl), -(C_1-C_2 alkyl)-(C_3-C_6 carbocyclyl), -(C_1-C_2 alkyl)-(5- to 10- membered heteroaryl), -(C_1-C_2 alkyl)-(5- to 10- membered heterocyclyl), or, together with R_3, represents $-(CH_2)_r-$ wherein r is from 2 to 4; and
- Het represents a 5- membered heteroaryl group containing 1 or 2 heteroatoms selected from N, O or S,

wherein:

- the alkyl and alkylene groups and moieties in the substituents R_2 and R_3 are unsubstituted and the alkyl groups and moieties in the substituents R_1 and R_4 are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_2 alkoxy, C_1-C_2 alkylthio, C_1-C_2 alkylamino and di(C_1-C_2 alkyl)amino substituents; and
- the aryl, heteroaryl, heterocyclyl and carbocyclyl groups and moieties in the substituents R_1, R_4 and Het are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, hydroxy, cyano, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy and C_1-C_4 haloalkylthio substituents.

Particularly preferred compounds of formula (II) are compounds of formula (IIa)



(IIa)

wherein:

- R_1 is hydrogen, an unsubstituted C_1-C_4 alkyl group, an unsubstituted cyclohexyl group or a phenyl group which is unsubstituted or substituted by 1, 2 or 3 substituents, preferably 1 or 2 substituents, selected from halogen,

cyano, C_1-C_2 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy and C_1-C_2 haloalkylthio substituents;

- each R_2 is the same or different and represents halogen, hydroxyl, amino, nitro or an unsubstituted C_1-C_2 alkyl, C_1-C_2 alkoxy, (C_1-C_2 alkyl)amino or di(C_1-C_2 alkyl)amino group, provided that not more than one R_2 substituent is nitro;
- R_4 represents hydrogen or an unsubstituted C_1-C_4 alkyl, phenyl or benzyl group;
- Het is a 5- membered heteroaryl group containing 1 or 2 heteroatoms selected from N, O and S, which is unsubstituted or substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_2 alkyl and C_1-C_2 haloalkyl substituents; and
- n is 0, 1 or 2.

Typically in the formula (IIa), each R_2 is the same or different and represents halogen, nitro or an unsubstituted C_1-C_2 alkyl or C_1-C_2 alkoxy group, provided that not more than one R_2 substituent is nitro.

Examples of the compounds of formula (II) are:

(S)-(4-Benzyloxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-3-(4-{[1-(5-Methyl-thiazol-2-yl)-ethylamino]-methyl}-phenoxymethyl) benzonitrile

(S)-(4-Benzyloxy-benzyl)-[1-(5-methyl-4,5-dihydro-oxazol-2-yl)-ethyl]-amine

(S)-3-(4-{[1-(5-Methyl-4,5-dihydro-oxazol-2-yl)-ethylamino]-methyl}-phenoxymethyl)-benzonitrile

(S)-(4-Benzyloxy-benzyl)-[1-(4-methyl-1H-imidazol-2-yl)-ethyl]-amine

(S)-[3-Methoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[2,6-Dimethoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[3-Methoxy-4-(3-methoxy-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[4-(2,6-Difluoro-benzyloxy)-3-methoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[2,6-Dimethoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[3-methyl-1-(5-methyl-thiazol-2-yl)-butyl]-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-(5-methyl-isoxazol-3-ylmethyl)-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-(1-methyl-1H-pyrrol-2-ylmethyl)-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-thiophen-3-ylmethyl-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-(1,3,5-trimethyl-1H-pyrazol-4-ylmethyl)-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-thiophen-2-ylmethyl-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-(3-methyl-thiophen-2-ylmethyl)-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[3-methyl-1-(5-methyl-thiazol-2-yl)-butyl]-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-[1-methyl-1H-pyrrol-2-ylmethyl)-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-thiophen-3-ylmethyl-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-(5-methyl-isoxazol-3-ylmethyl)-amine

(S)-[2,6-Dimethoxy-4-(4-trifluoromethyl-benzyloxy)-benzyl]-[3-methyl-1-(5-methyl-thiazol-2-yl)-butyl]-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine

(S)-[2,6-Dimethoxy-4-(4-trifluoromethyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine

(S)-[4-(2-Fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine

(S)-(4-Benzyloxy-benzyl)-[3-methyl-1-(5-methyl-thiazol-2-yl)-butyl]-amine

(S)-(4-Benzyloxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine

(S)-(4-Benzyloxy-3-methoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Methoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Cyclohexylmethoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-3-chloro-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-2-methoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-2,6-dimethoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]amine

(S)-(4-Benzyloxy-2-chloro-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-3-ethoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-3-nitro-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[4-(2,6-Difluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-3,5-dimethoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-(3-methyl-thiophen-2-ylmethyl)-amine

[2,6-Dimethoxy-4-(2,4,6-trifluoro-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(4-Benzyloxy-3-methyl-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

2-Benzyloxy-5-{[1-(5-methyl-thiazol-2-yl)-ethylamino]-methyl}-phenylamine

[4-(4-Fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

[3-Chloro-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

[3-Chloro-4-(2-chloro-6-fluoro-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

[1-(5-Methyl-thiazol-2-yl)-ethyl]-[3-nitro-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-amine

[2-Chloro-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

[2-Chloro-4-(2-chloro-6-fluoro-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

[4-(2-Chloro-6-fluoro-benzyloxy)-3-nitro-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

[2-Methoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

and pharmaceutically acceptable salts thereof.

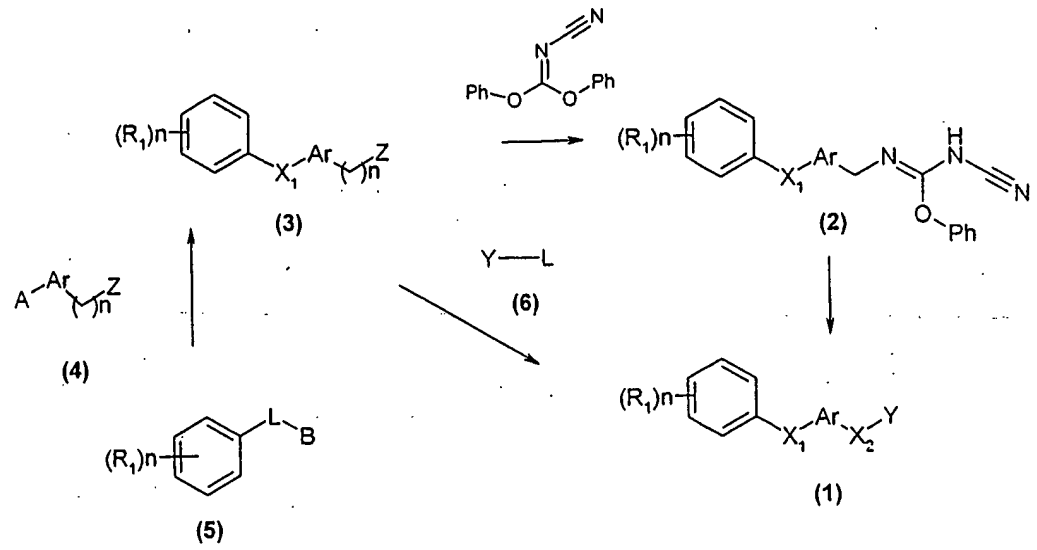
As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids such as hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases such as alkyl amines, aralkyl amines or heterocyclic amines.

The compounds of the invention can contain one or more chiral centre. For the avoidance of doubt, the chemical structures depicted herein are intended to embrace all stereoisomers of the compounds shown, including racemic and non-racemic mixtures and pure enantiomers and/or diastereoisomers.

Preferred compounds of the invention are optically active isomers. Thus, for example, preferred compounds of formula (I) or formula (II) containing only one chiral centre include an R enantiomer in substantially pure form, an S enantiomer in substantially pure form and enantiomeric mixtures which contain an excess of the R enantiomer or an excess of the S enantiomer.

The compounds of formula (I) may be prepared by conventional routes, for example those set out in any of schemes 1 to 4 shown below. In the reaction schemes shown below, R_1, n, X_1, Ar, X_2 and Y are as defined above for the formula (I), unless otherwise indicated.

Scheme 1



Compounds of formula (1) in which R_1, n, X_1 and Ar are defined as above and X_2 is CH_2NH (reaction scheme 1) may be prepared from compounds of formula (2) by cyclisation in the presence of an amine, for example hydrazine hydrate. Compounds of formula (2) may be prepared by treating compounds of formula (3), in which n is 1, with diphenyl cyanocarbonimidate.

Alternatively, compounds of formula (1) where R_1, n, X_1, Ar and Y are defined as above and X_2 is $-L''-NR'-$, $-L''-O-$ or $-L''-S-$, wherein L'' is a C_1-C_4 alkylene group, may be prepared from compounds of formula (3) in which n is from 1 to 4 and Z is a leaving group, preferably chlorine, and compounds of formula (6) where L is NHR', OH or SH and Y is as defined above, using standard methods familiar to those skilled in the art. Such methods include alkylation in the presence of a base, for example triethylamine.

Compounds of formula (1) in which R_1, n, X_1, Ar and Y are defined as above and X_2 is $-L''-NR'-$ in which L'' represents a direct bond may be prepared from compounds of formula (3) in which n = 0 and Z is a leaving group, for example a halogen such as bromine, and compounds of formula (6) where L is NHR' and Y is as defined above, using standard methods familiar to those skilled in the art. Such methods include Buchwald type palladium-mediated cross coupling.

Compounds of formula (1) in which R_1, n, X_1, Ar and Y are defined as above and X_2 is -L″-S- in which L″ is a direct bond may be prepared from compounds of formula (3) where n = 0 and Z is a leaving group, for example a halogen such as bromine, and compounds of formula (6) where L is SH, using standard methods familiar to those skilled in the art. Such methods include alkylation in the presence of base.

Compounds of formula (1) in which R_1, X_1, n, Ar and Y are defined as above and X_2 is -L″-O- in which L″ is a direct bond may be prepared from compounds of formula (3) in which n = 0 and Z is OH and compounds of formula (6) where L is OH and Y is as defined above, using standard methods familiar to those skilled in the art. Such methods include the Mitsunobu reaction.

Compounds of formula (3) in which Ar is defined as above and X_1 is -L-O-L′-, -L-NR′-L′- or -L-S-L′- wherein L′ is as defined above and L is a C_1-C_4 alkylene group may be prepared from compounds of formula (4) in which A is -L′-OH, -L′-SH or -L′-NHR′ and compounds of formula (5) in which L is a C_1-C_4 alkylene group and B is a leaving group, preferably a halogen such as bromine, by standard methods familiar to those skilled in the art. Such methods include alkylation in the presence of a base.

Compounds of formula (3) in which Ar is defined as above and X_1 is -L-NR′-L′- wherein L′ is as defined above and L represents a direct bond may be prepared from compounds of formula (4) where A is -L′NHR′ and compounds of formula (5) where L is a direct bond and B is a halogen such as bromine, by standard methods familiar to those skilled in the art. Such methods include palladium-mediated cross coupling as per the Buchwald reaction.

Compounds of formula (3) in which Ar is defined as above and X_1 is -L-O-L′- wherein L′ is as defined above and L represents a direct bond may be prepared from compounds of formula (4) where A is -L′OH and compounds of formula (5) wherein L is a direct bond and B is OH, by standard methods familiar to those skilled in the art. Such methods include the Mitsunobu reaction. Alternatively, such compounds may be prepared from compounds of formula (4) where A is -L′OH and compounds of formula (5) where L is a direct bond and B is a halogen such a

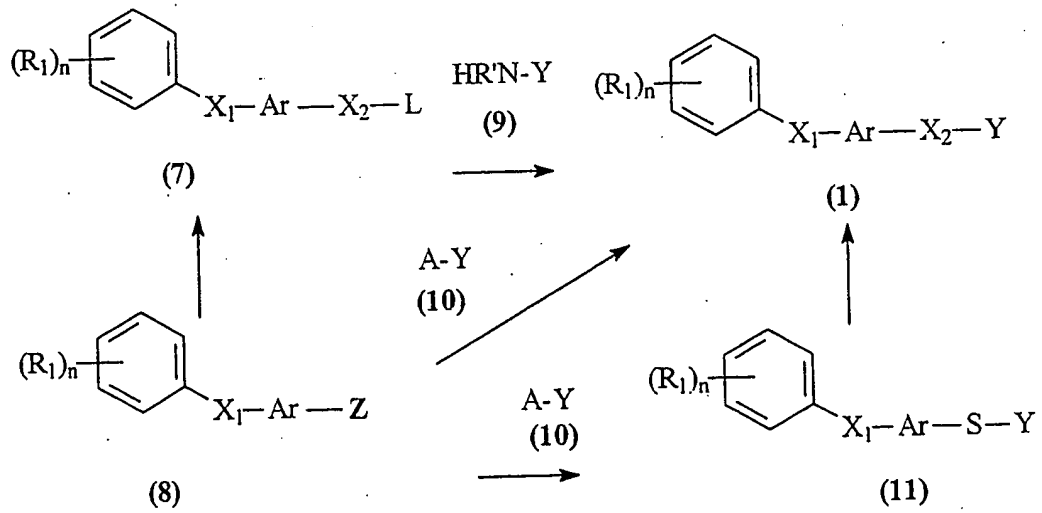
bromine, by standard methods familiar to those skilled in the art. Such methods include the Ullman reaction.

Compounds of formula (3) in which Ar is defined as above and X_1 is -L-S-L'- wherein L' is as defined above and L represents a direct bond may be prepared from compounds of formula (4) where A is -L'SH and compounds of formula (5) where L is a direct bond and B is a halogen such as bromine, by standard methods familiar to those skilled in the art. Such methods include alkylation as described above.

Compounds of formula (3) in which Ar is defined as above and X_1 is a direct bond may be prepared from compounds of formula (4) where A is bromine and compounds of formula (5) where B is a boronic acid residue (-$B(OH)_2$), by standard methods familiar to those skilled in the art. Such methods include the Suzuki reaction.

Compounds of formulae (4), (5) and (6) are known compounds or may be prepared from known compounds by analogy with known methods.

Scheme 2



Compounds of formula (1) in which X_2 is -CONR'-, -SONR'- or -$S(O)_2$NR'- (reaction scheme 2) may be prepared by treating compounds of formula (7), in which X_2 is -CO-, -SO-, or -$S(O)_2$- and L is OH or Cl, with compounds of formula (9) in which Y is defined as above, under standard amide coupling reaction

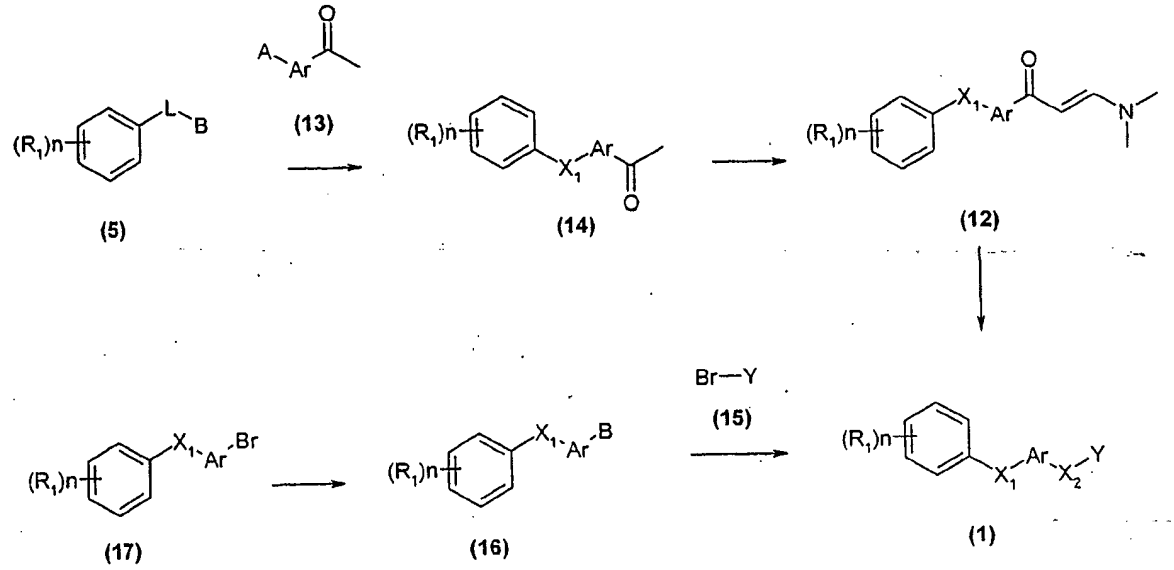
conditions. Typically, when L is Cl, the reaction is effected in the presence of a base such as triethylamine. The compounds of formula (7) are known compounds, or can be prepared from known compounds by analogy with known methods. For example, compounds of formula (7) in which X_2 is SO_2 and L is Cl can be prepared from corresponding compounds of formula (8) in which Z is H, in the presence of chloro sulphonic acid.

Compounds of formula (1) in which X_2 is -CO- may be prepared from compounds of formula (8) in which Z is H and compounds of formula (10) where Y is as defined above and A is COCl by standard methods. Such methods include the Friedel Crafts reaction. Compounds of formula (1) in which X_2 is $-CO_2-$ may be prepared from compounds of formula (8) in which Z is OH and compounds of formula (10) in which Y as defined above and A is CO_2H by standard methods familiar to those skilled in the art. They may also, of course, be prepared from compounds of formula (8) in which Z is $-CO_2H$ and compounds of formula (10) in which Y is as defined above and A is OH by standard methods familiar to those of skill in the art. Such methods include esterification by conventional techniques.

Compounds of formula (1) in which X_2 is -SO- or $-SO_2-$ may be prepared from compounds of formula (11) by standard methods familiar to those skilled in the art. Such methods include oxidation in the presence of 3-chloroperoxybenzoic acid (mCPBA). Compounds of formula (11) may be prepared from compounds of formula (8) in which Z is a leaving group, preferably a halogen such as bromine, and compounds of formula (10) in which A is SH, by standard methods. Such methods include alkylation as described above.

Compounds of formulae (8), (9) and (10) are known compounds or may be produced from known compounds by analogy with known methods.

Scheme 3



Compounds of formula (1) in which R_1, n, X_1 and Ar are defined as above and X_2 is a direct bond (reaction scheme 3), can be prepared by treating compounds of formula (12) with a nucleophile, for example hydrazine hydrate. Compounds of formula (12) can be prepared from known compounds by analogy with known methods. For example compounds of formula (12) can be prepared from the corresponding compounds of formula (14) and dimethylformamide dimethyl acetal.

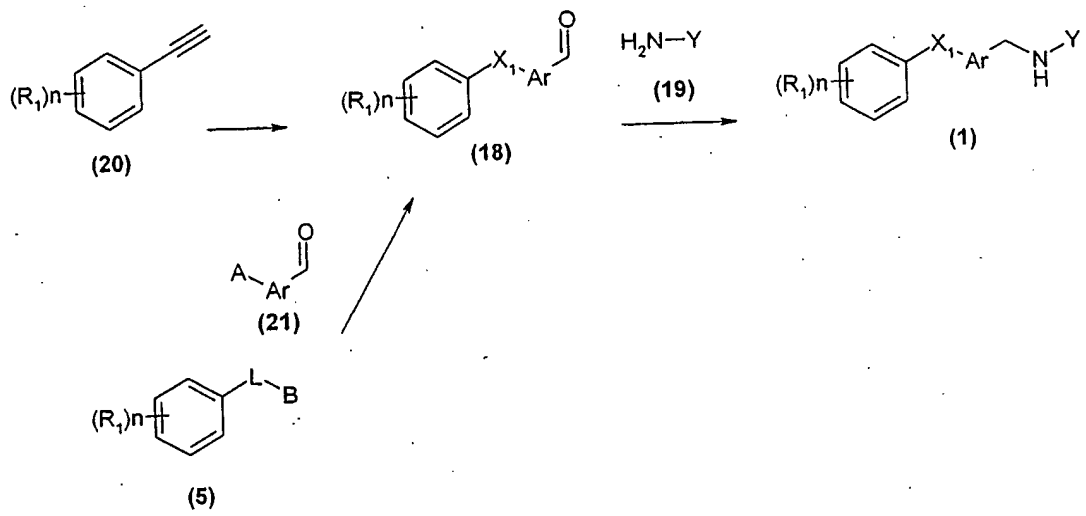
Compounds of formula (14) can be prepared by processes similar to those set out above for the preparation of the compounds of formula (3). Thus, for example, compounds of formula (14) in which Ar is defined as above and X_1 is -L-O-L′-, -L-NR′-L′- or -L-S-L′- wherein L′ is as defined above and L represents a C_1-C_4 alkylene group may be prepared from compounds of formula (13) in which A is L′-OH, L′-SH or L′NHR′ and compounds of formula (5) in which B is a leaving group, preferably a halogen such as bromine, by standard methods familiar to those skilled in the art. Such methods include alkylation in the presence of a base.

Alternatively, compounds of formula (1) in which R_1, n, X_1, Ar and Y are as defined above and X_2 is a direct bond can be prepared from compounds of formula (15) and compounds of formula (16), in which B is a boronic acid residue ($B(OH)_2$) by standard methods such as the Suzuki reaction. Such compounds can also be prepared from compounds of formula (15) and compounds of formula (16) where L

is tributyl tin ($Sn(C_4H_9)_3$) by standard methods. Such methods include the Stille reaction.

Compounds of formula (16) in which B is $-B(OH)_2$ can be prepared from the corresponding bromo-substituted compound of formula (17) in the presence of triethylborate ester. Compounds of formula (16) where L is $Sn(C_4H_9)_3$ can be prepared from the corresponding bromo-substituted compound of formula (17) and tributyl tin chloride in the presence of butyl lithium. Compounds of formula (17) are known compounds or may be produced from known compounds by analogy with known methods. They may, for example, be prepared by processes similar to those set out above for the preparation of compounds of formula (3). Further, compounds of formulae (13) and (15) are also known compounds or can be prepared by analogy with known methods.

Scheme 4



Compounds of formula (1) in which Ar is a heterocycle, X_2 is CH_2NH and Y is as defined above (reaction scheme 4) may be prepared from compounds of formulae (18) and (19) by standard methods. Such methods include reductive amination in the presence of a reducing agent, for example sodium cyanoborohydride.

Compounds of formula (18) in which Ar is as defined above are known compounds or can be prepared from known compounds by analogy with known methods. For example, a compound of formula (18) in which X_1 is a direct bond and

Ar is 2H-[1,2,3]-triazole may be prepared from compounds of formula (20) as described in M. Journet et al, Tetrahedron Letters, 42, 2001.

Compounds of formula (18) in which Ar is defined as above and X_1 is -L-O-L′-, -L-NR′-L′- or -L-S-L′- wherein L′ is as defined above and L is a C_1-C_4 alkylene group, may be prepared from compounds of formula (21) in which A is -L′-OH, -L′-SH or -L′NHR′ and compounds of formula (5) where B is a leaving group, preferably a halogen such as bromine, by standard methods familiar to those skilled in the art. Such methods include alkylation in the presence of base. Compounds of formula (18) where Ar is defined as above and X_1 is -L-NR′-L′ wherein L′ is as defined above and L represents a direct bond may be prepared from compounds of formula (21) where A is -L′NHR′ and compounds of formula (5) where L is a direct bond and B is bromine, by standard methods familiar to those skilled in the art. Such methods include palladium-mediated cross coupling as per the Buchwald reaction.

Compounds of formula (18) in which Ar is defined as above and X_1 is -L-O-L′ wherein L′ is as defined above and L represents a direct bond may be prepared from compounds of formula (21) where A is -L′OH and compounds of formula (5) where L is a direct bond and B is OH, by standard methods familiar to those skilled in the art. Such methods include the Mitsunobu reaction. Compounds of formula (18) in which Ar is defined as above and X_1 is -L-S-L′- wherein L′ is as defined above and L represents a direct bond may be prepared from compounds of formula (21) where A is -L′SH and compounds of formula (5) where L is a direct bond and B is halogen such as bromine, by standard methods familiar to those skilled in the art. Such methods include alkylation as described above.

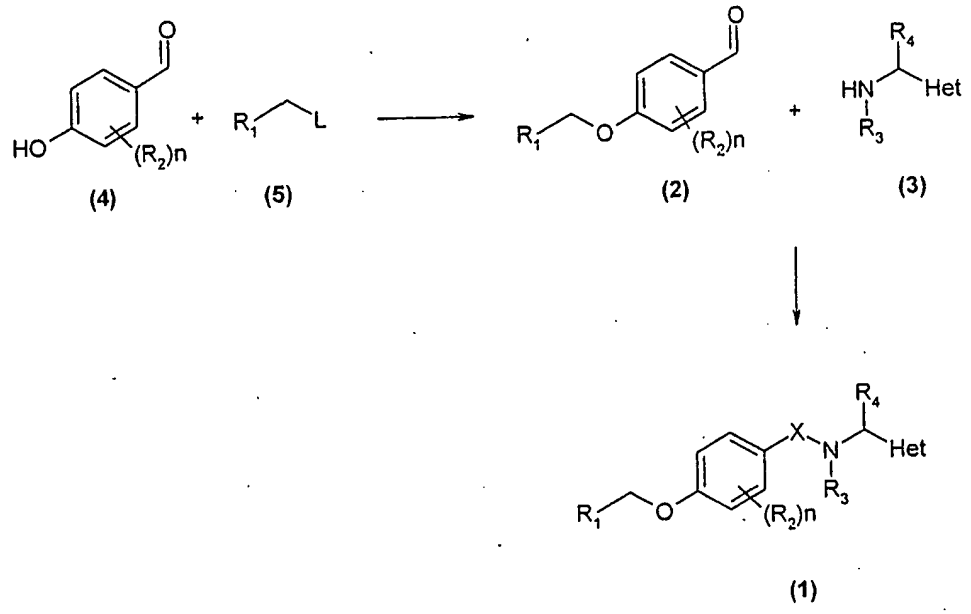
Compounds of formula (18) in which Ar is defined as above and X_1 is a direct bond may be prepared from compounds of formula (21) where A is bromine and compounds of formula (5) where B is a boronic acid residue (-$B(OH)_2$), by standard methods familiar to those skilled in the art. Such methods include the Suzuki reaction. Compounds of formulae (20), (21) and (19) are known compounds or can be prepared by analogy with known methods. For example, compounds of formula (19) in which Y is a heterocycle are known compounds or can be prepared from known compounds by analogy with known methods as described in

'Heterocyclic Chemistry', 4th Edition, J. A. Joule and K. Mills, Blackwells, Oxford, 2000.

The thus obtained compounds of formula (I) may be salified by treatment with an appropriate pharmaceutically acceptable acid or base to form a pharmaceutically acceptable salt, as described above. Racemic mixtures obtained by any of the above processes can be resolved by standard techniques, for example elution on a chiral chromatography column.

The compounds of formula (II) may also be prepared by conventional routes, for example those set out in any of schemes A to H shown below. In the reaction schemes shown below, R_1, n, R_2, R_3, R_4, X and Het are as defined above for the formula (II), unless otherwise indicated.

Scheme A



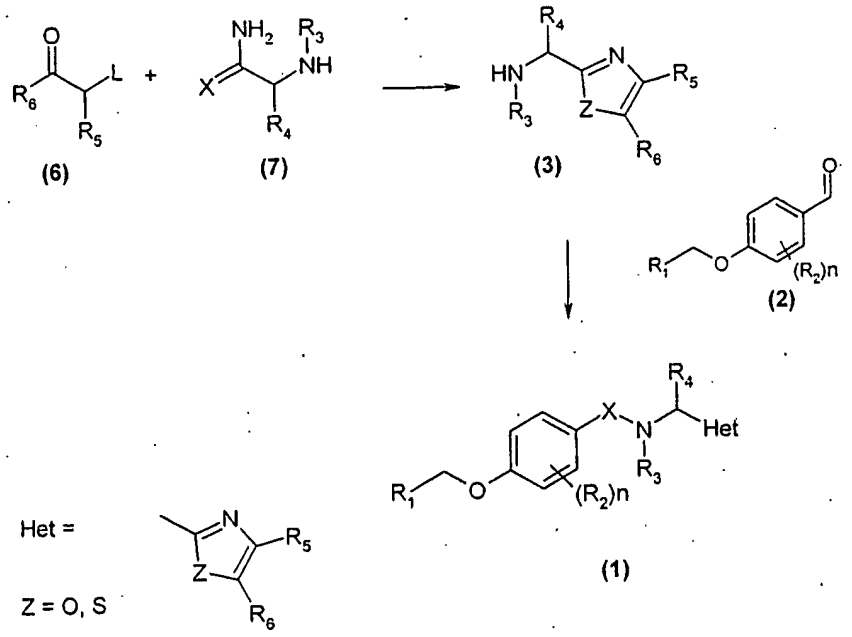
Compounds of formula (II) where X is CH_2 and R_1 to R_4 and Het are defined as above (reaction scheme A) may be prepared from aldehydes (2) and heterocyclic amines (3) using standard methods such as reductive amination in the presence of a reducing agent, for example sodium cyanoborohydride. Typically the reaction is performed in a solvent such as methanol, tetrahydrofuran or dichloromethane at room temperature in a "one pot" reaction. Aldehydes (2) are known compounds or

can be prepared by analogy with known methods. For example, they may be prepared by reaction of hydroxybenzaldehydes (4) and compounds of formula (5) in which L is a leaving group, for example chloride, by standard methods familiar to those skilled in the art such as alkylation in the presence of a base.

The aldehydes (2) may also be prepared from hydroxybenzaldehydes (4) and compounds of formula (5) in which L is OH converted into a better leaving group by standard methods such as mesylation. Alternatively, aldehydes (2) may be prepared from hydroxybenzaldehydes (4) and compounds of formula (5) in which L is OH by standard methods such as Mitsunobu reaction.

Compounds of formula (3) are known compounds, or can be prepared by analogy with known methods. Schemes 2 to 4 detail examples of appropriate synthetic techniques for preparing the compounds of formula (3).

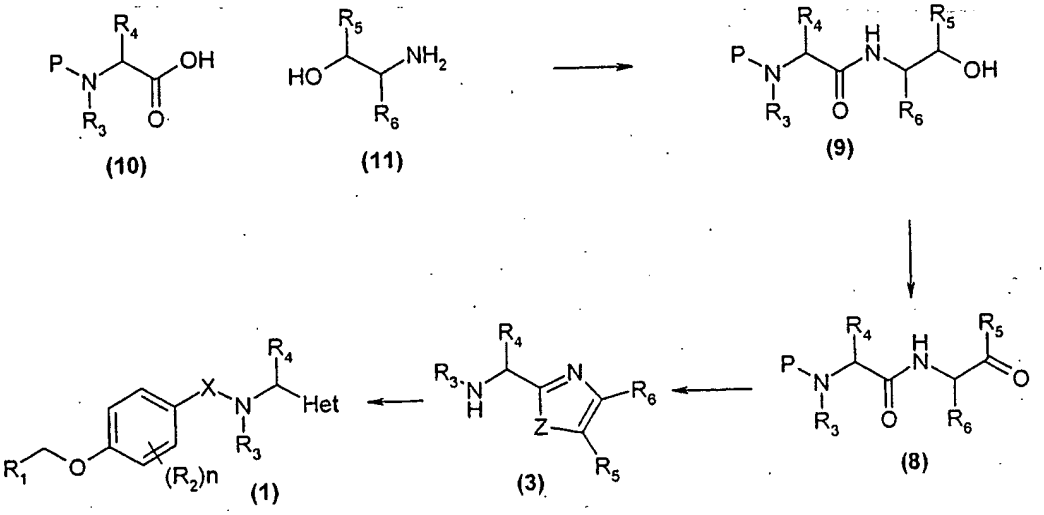
Scheme B



Scheme B details an example of the preparation of a heterocyclic amine (3) wherein Het is as depicted above and Z is O or S. X in the formula (7) is of course also O or S. R_5 and R_6 in scheme (B) (and indeed in subsequent schemes) represent substituents on the Het moiety. Accordingly, they can represent any of the groups mentioned above as appropriate substituents for the moiety Het.

The synthesis is effected by analogy with known methods, (see, for example, "Heterocyclic Chemistry", 4th Edition, J. A. Joule and K. Mills, Blackwells, Oxford, **2000**). The heterocyclic amines may be prepared from a ketone (6), where L is a leaving group, preferably bromide, and an amide (7), where X is O or S by standard methods familiar to those skilled in the art.

Scheme C

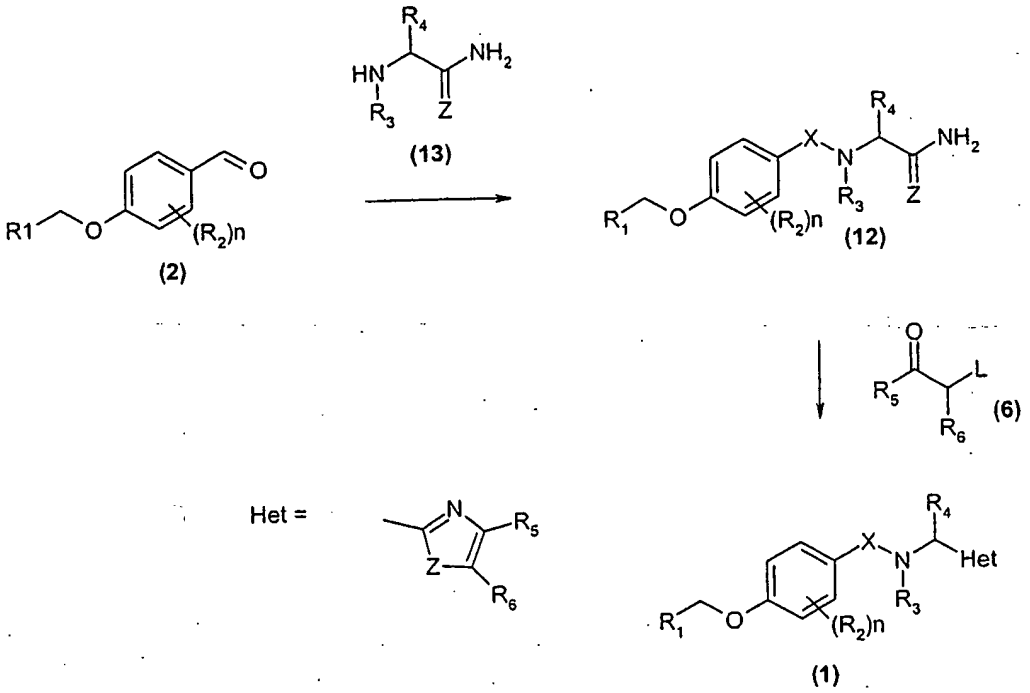


Scheme C details an example of the preparation of a heterocyclic amine (3) wherein Het is as depicted in the formula (3) above and Z is NH, O or S. Such amines may be prepared from amines (8) where P is a protecting group. Examples of suitable protecting groups can be found in 'Protecting Groups' PJ Kocienski, Thieme Medical Publishers **2000.** P is preferably CBz. The amines (3) can be prepared from the amines (8) by cyclisation in the presence of ammonium acetate, acetonitrile or Lawesson's reagent.

The amines (8) may be prepared from compounds of formula (9) by standard methods such as oxidation using Dess-Martin periodinane. Compounds of formula (9) may be prepared from amino acids (10) and amino alcohols (11) under suitable standard amide coupling reaction conditions.

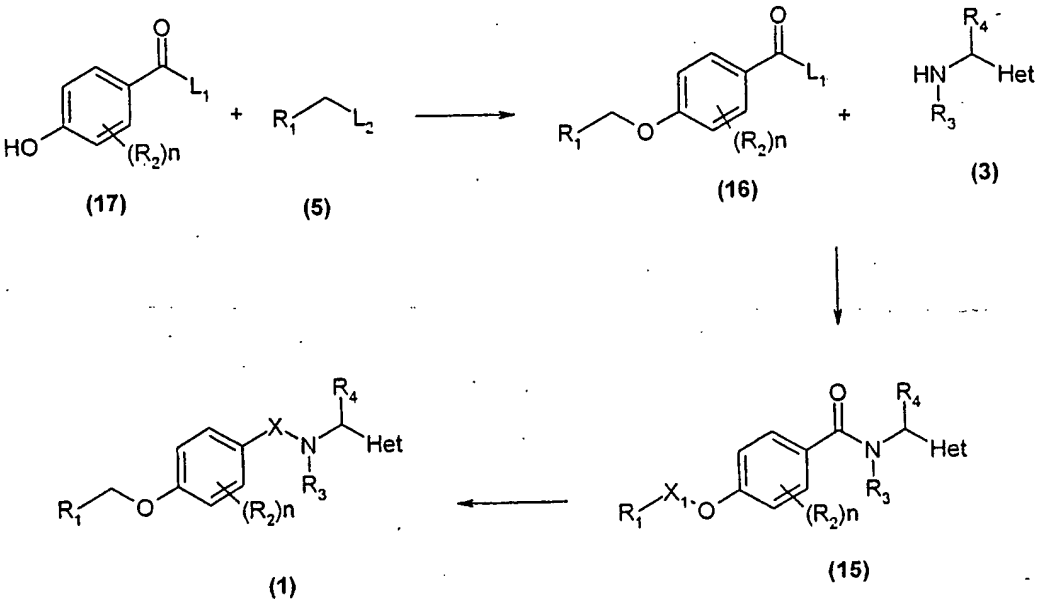
Heterocyclic amines (3) where Z is substituted N may be prepared from heterocyclic amines (3) where Z is NH by standard methods familiar to those skilled in the art such as alkylation in the presence of a base, for example sodium hydride.

Scheme D



Scheme D depicts a further example of an appropriate process for preparing a compound of formula (II) where X is CH_2, R_1 to R_4 are as defined above, Het is as depicted above and Z is O or S. Such compounds may be prepared from compounds of formula (12) and α-haloketones (6) where L is a leaving group, preferably bromide, by cyclisation in the presence of base. The amides (12) may be prepared from compounds of formula (13) and aldehydes (2) by standard methods such as reductive amination using in the presence of a reducing agent.

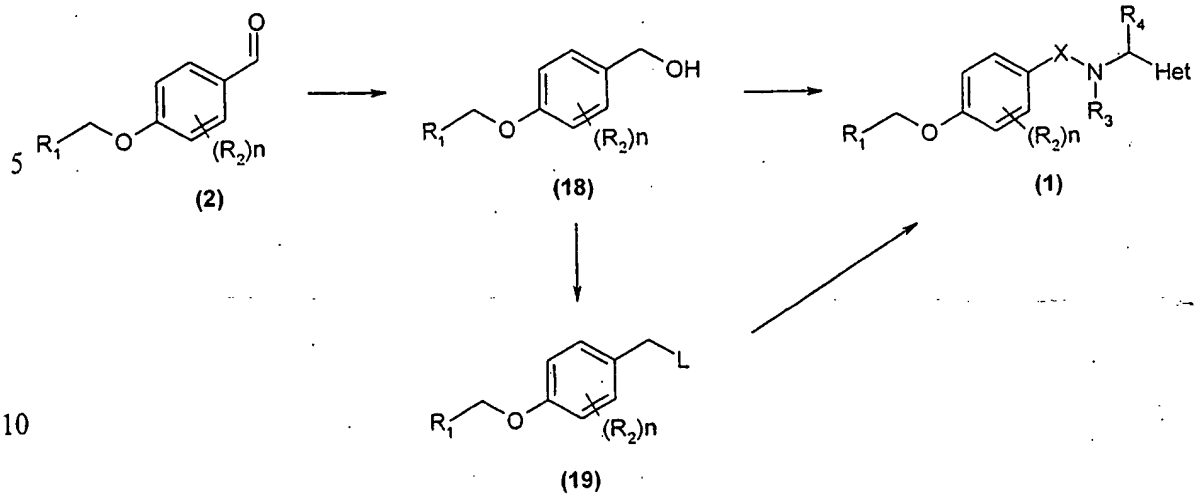
Scheme E



Compounds of formula (II) wherein X is $-CH_2-$ and R_1 to R_4 and Het are defined as above (reaction scheme E) may also be prepared from amides (15) by standard methods such as reduction with borane. Amides (15) may be prepared from heterocyclic amines (3) and compounds with the formula (16), in which L_1 represents OH or Cl, under standard amide coupling reaction conditions. Typically, where L_1 is OH, the reaction is effected in the presence of a coupling agent such as EDC/HOBT, HATU or HBTU. The amines (3) are known compounds or can be prepared by analogy with known methods.

Compounds with the general formula (16) in which L_1 is a leaving group, for example a chlorine atom, may be prepared by standard methods, such as alkylation of compounds (17) as described previously.

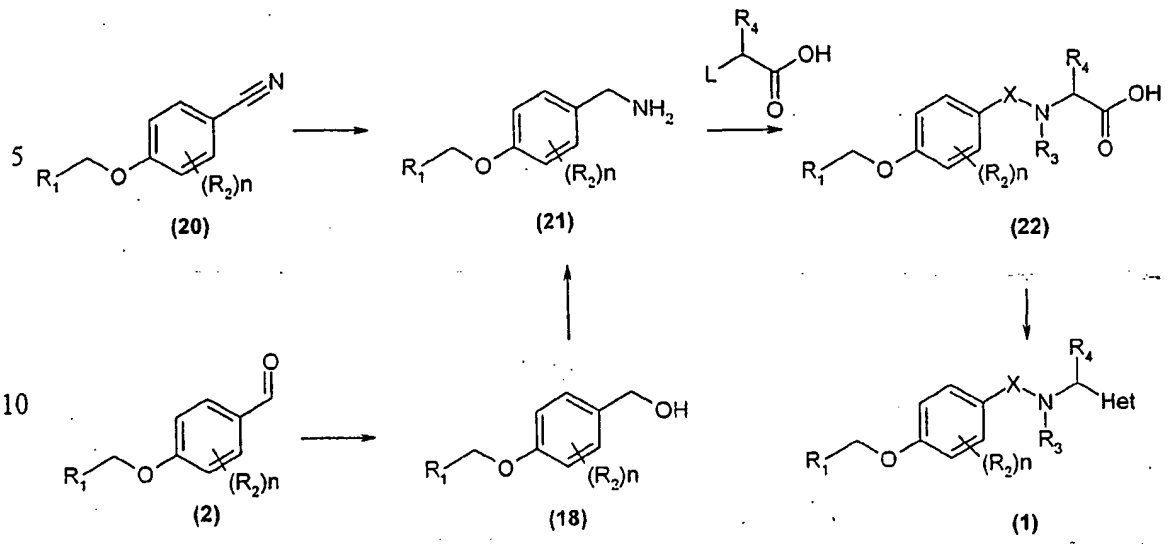
Scheme F



Compounds of formula (II) wherein X is CH_2 and R_1 to R_4 and Het are defined as above (reaction scheme F) may also be prepared from alcohols (18) by standard methods such as Mitsunobu reaction in the presence of an appropriate amine. Alternatively, compounds of formula (II) may be prepared from alcohols (18) by standard methods such as converting the alcohol into a better leaving group such as a mesylate followed by alkylation in the presence of the appropriate amine. Alcohols (18) may be prepared from aldehydes (2) by standard methods familiar to those skilled in the art such as reduction in the presence of borane.

Alternatively, compounds of formula (II) may be prepared from compounds of formula (19) wherein L is a leaving group, for example chlorine, by standard methods such as alkylation with an appropriate amine. Appropriate reaction conditions for such alkylations are given above. Compounds of formula (19), wherein L is a leaving group, may be prepared from alcohols (18) by standard methods such as halogenation in the presence of a thionyl halide for example thionyl chloride.

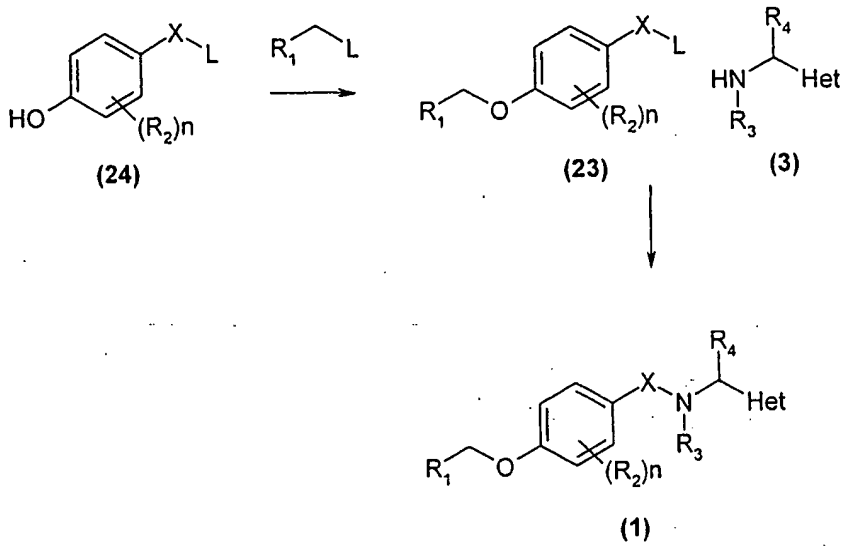
Scheme G



Compounds of formula (II) where X is CH_2, R_3 is hydrogen, R_1, R_2 and R_4 are as defined above and Het is as depicted in scheme B may also be prepared from compounds of formula (22), in which A is a direct bond or a C_1-C_6 alkyl group (reaction scheme G). The reaction can be effected by standard methods familiar to those skilled in the art (see for example those set out in reaction scheme 2 for the preparation of compounds of formula (3)).

Compounds of formula (22) may be prepared from amines (21) by standard methods such as alkylation with haloacids in the presence of base. Amines of formula (21) may be prepared from nitriles (20) by standard methods such as reduction with borane. The preparation of nitriles (20) is described in the literature. Alternatively, amines (21) may be prepared from alcohols (18) by standard methods such as Mitsunobu reaction with phthalimide followed by deprotection with hydrazine.

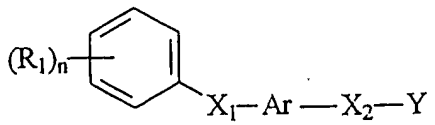
Scheme H



Compounds of formula (II) in which X is -CO-, -SO- or -S(O)$_2$- and R_1 to R_4 and Het are defined as above (reaction scheme H) can be prepared by reacting compounds of formula (23), in which L is OH or Cl, with heterocyclic amines (3) under standard amide coupling reaction conditions. Typically, when L is OH, the reaction is effected in the presence of a coupling agent such as EDC/HOBT, HATU or HBTU. The compounds of formula (23) are known compounds, or can be prepared by analogy with known methods. For example, they can be prepared from corresponding compounds of formula (24) by standard methods, such as those set out in reaction scheme 1 for the preparation of compounds of formula (2).

The thus obtained compounds of formula (II) may be salified by treatment with an appropriate acid or base. Racemic mixtures obtained by any of the above processes can be resolved by standard techniques, for example elution on a chiral chromatography column.

The compounds of the invention are therapeutically useful. The present invention therefore also provides a compound of formula (I') or a pharmaceutically acceptable salt thereof, for use in the treatment of the human or animal body



(I')

wherein:

- each R_1 is the same or different and represents halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, hydroxy, amino, C_1-C_6 alkylamino or di-(C_1-C_6 alkyl)amino;
- n is 0, 1, 2 or 3;
- X_1 represents a direct bond, -L-O-L'-, -L-S-L'- or -L-NR'-L'- wherein L and L' are the same or different and each represent a direct bond or C_1-C_4 alkylene group and R' represents hydrogen or C_1-C_4 alkyl;
- Ar represents a 5- to 6- membered heteroaryl group or a phenyl group which is optionally fused to a 5- membered heteroaryl group;
- X_2 represents a direct bond, -L''-O-, -L''-S-, L''-NR'-, -CO-, -CO_2-, -S(O)-, -$S(O)_2$-, -CO-NR'-, -S(O)-NR'- or -$S(O)_2$-NR'-, wherein L'' represents a direct bond or C_1-C_4 alkylene group and R' represents hydrogen or C_1-C_4 alkyl; and
- Y represents -L'''-NR'R'' or a -(C_1-C_6 alkyl)-(5- to 10- membered heteroaryl), -(C_1-C_6 alkyl)-(5- to 10- membered heterocyclyl), -(C_1-C_6 alkyl)-phenyl, phenyl, 5- to 10- membered heteroaryl or 5- to 10- membered heterocyclyl group, wherein L''' is a C_1-C_4 alkylene group and R' and R'' are the same or different and each represent hydrogen, C_1-C_6 alkyl or phenyl, provided that (a) when Y is a 5- to 10- membered heteroaryl group it is other than a pyridyl group and (b) when X_1 is -O-, -S- or -NR'-, X_2 is a direct bond and Y is a 5- to 10- membered heteroaryl group which contains 1 or 2 heteroatoms selected from N, O and S, the 5- to 10- membered heteroaryl group is attached via a carbon atom which is not adjacent to a N atom,

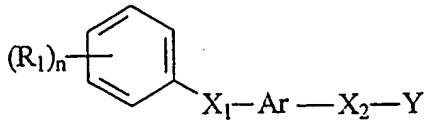
wherein:

- the alkyl and alkylene groups and moieties in the substituents R_1, X_1, X_2 and Y are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylamino and di(C_1-C_4 alkyl)amino substituents; and
- the phenyl, heteroaryl and heterocyclyl groups in the substituents Ar_1 and Y are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy,

C_1-C_6 alkylthio, hydroxy, -$NR'R''$, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 haloalkylthio, cyano, -$CONR'R''$, -$S(O)_2$-$NR'R''$, -CO_2-R'', -$S(O)_2R''$ and phenyl substituents, wherein R' and R'' are the same or different and each represent hydrogen or C_1-C_4 alkyl,

provided that the compound of formula (I') is other than 4-[4-(benzyloxy)phenyl]-1H-pyrazole.

Further, certain compounds of the formula (I) are believed to be novel. The present invention therefore also provides a compound of formula (I") or a pharmaceutically acceptable salt thereof.



(I")

wherein:

- each R_1 is the same or different and represents halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, hydroxy, C_1-C_6 alkylamino or di-(C_1-C_6 alkyl)amino;
- n is 0, 1, 2 or 3;
- X_1 represents a direct bond, -L-O-L'-, -L-S-L'- or -L-NR'-L'- wherein L and L' are the same or different and each represent a direct bond or C_1-C_4 alkylene group and R' represents hydrogen or C_1-C_4 alkyl;
- Ar represents a 5- to 6- membered heteroaryl group or a phenyl group which is optionally fused to a 5- membered heteroaryl group;
- X_2 represents a direct bond, -L''-O-, -L''-S-, L''-NR'-, -CO-, -CO_2-, -S(O)-, -$S(O)_2$-, -CO-NR'-, -S(O)-NR'- or -$S(O)_2$-NR'-, wherein L'' represents a direct bond or C_1-C_4 alkylene group and R' represents hydrogen or C_1-C_4 alkyl; and
- Y represents -L'''-$NR'R''$ or a -(C_1-C_6 alkyl)-(5- to 10- membered heteroaryl), -(C_1-C_6 alkyl)-(5- to 10- membered heterocyclyl), -(C_1-C_6 alkyl)-phenyl, phenyl, 5- to 10- membered heteroaryl or 5- to 10- membered heterocyclyl group, wherein L''' is a C_1-C_4 alkylene group and R' and R'' are the same or different and each represent hydrogen, C_1-C_6 alkyl or phenyl, provided that

(a) when Y is a 5- to 10- membered heteroaryl group it is other than a pyridyl group and (b) when X_1 is -O-, -S- or -NR'-, X_2 is a direct bond and Y is a 5- to 10- membered heteroaryl group which contains 1 or 2 heteroatoms selected from N, O and S, the 5- to 10- membered heteroaryl group is attached via a carbon atom which is not adjacent to a N atom,

wherein:

- the alkyl and alkylene groups and moieties in the substituents R_1, X_1, X_2 and Y are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylamino and di(C_1-C_4 alkyl)amino substituents; and
- the phenyl, heteroaryl and heterocyclyl groups in the substituents Ar_1 and Y are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, hydroxy, -$NR'R''$, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 haloalkylthio, cyano, -$CONR'R''$, -$S(O)_2$-$NR'R''$, -CO_2-R'', -$S(O)_2R''$ and phenyl substituents, wherein R' and R'' are the same or different and each represent hydrogen or C_1-C_4 alkyl,

provided that the compound of formula (I") is other than 4-[4-(benzyloxy)phenyl]-1H-pyrazole.

Preferred compounds of formulae (I') and (I") are the same as the preferred compounds of formula (I) set out above. In particular, the compound of formula (I') or (I") may be a compound of formula (Ia), (Ib) or (Ic) as defined above, as long as it is not 4-[4-(benzyloxy)phenyl]-1H-pyrazole.

Preferably, in the compounds of formulae (I') and (I"), when X_1 is -O- or -CH_2-O-, Y is other than a phenyl-substituted thiazolyl group. More preferably, Y is other than a phenyl-substituted thiazolyl group whatever X_1 represents. Most preferably, Y in the formulae (I') and (I") is other than a phenyl-substituted heteroaryl group.

The present invention also provides a compound of the formula (II), or a pharmaceutically acceptable salt thereof, for use in the treatment of the human or animal body. Further, certain compounds of the formula (II) are believed to be

novel. The present invention therefore also provides a compound of formula (II), as defined above, or a pharmaceutically acceptable salt thereof, provided that Het in the formula (II) is other than furanyl.

The present invention also provides a pharmaceutical composition comprising (a) a compound of the formula (I'), as defined above, a compound of the formula (II), as defined above, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable carrier or diluent. Said pharmaceutical composition typically contains up to 85 wt% of a compound of the invention. More typically, it contains up to 50 wt% of a compound of the invention. Preferred pharmaceutical compositions are sterile and pyrogen free. Further, the pharmaceutical compositions provided by the invention typically contain a compound of the invention which is a substantially pure optical isomer.

The compounds of the invention may be administered in a variety of dosage forms. Thus, they can be administered orally, for example as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules. Preferred pharmaceutical compositions of the invention are compositions suitable for oral administration, for example tablets and capsules.

Compositions suitable for oral administration may, if required, contain a colouring or flavoring agent. Typically, a said capsule or tablet comprises from 5 to 500 mg, preferably 10 to 500 mg, more preferably 15 to 100 mg, of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The compounds of the invention may also be administered parenterally, whether subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques. The compounds may also be administered as suppositories.

One preferred route of administration is inhalation. The major advantages of inhaled medications are their direct delivery to the area of rich blood supply in comparison to many medications taken by oral route. Thus, the absorption is very rapid as the alveoli have an enormous surface area and rich blood supply and first pass metabolism is bypassed.

Preferred pharmaceutical compositions of the invention therefore include those suitable for inhalation. The present invention also provides an inhalation device containing such a pharmaceutical composition. Typically said device is a

metered dose inhaler (MDI), which contains a pharmaceutically acceptable chemical propellant to push the medication out of the inhaler. Typically, said propellant is a fluorocarbon.

Further preferred inhalation devices include nebulizers. Nebulizers are devices capable of delivering fine liquid mists of medication through a "mask" that fits over the nose and mouth, using air or oxygen under pressure. They are frequently used to treat those with asthma who cannot use an inhaler, including infants, young children and acutely ill patients of all ages.

Said inhalation device can also be, for example, a rotary inhaler or a dry powder inhaler, capable of delivering a compound of the invention without a propellant.

Typically, said inhalation device contains a spacer. A spacer is a device which enables individuals to inhale a greater amount of medication directly into the lower airways, where it is intended to go, rather than into the throat. Many spacers fit on the end of an inhaler; for some, the canister of medication fits into the device. Spacers with withholding chambers and one-way valves prevent medication from escaping into the air. Many people, especially young children and the elderly, may have difficulties coordinating their inhalation with the action necessary to trigger a puff from a metered dose inhaler. For these patients, use of a spacer is particularly recommended.

Another preferred route of administration is intranasal administration. The nasal cavity's highly permeable tissue is very receptive to medication and absorbs it quickly and efficiently, more so than drugs in tablet form. Nasal drug delivery is less painful and invasive than injections, generating less anxiety among patients. Drugs can be delivered nasally in smaller doses than medication delivered in tablet form. By this method absorption is very rapid and first pass metabolism is bypassed, thus reducing inter-patient variability. Nasal delivery devices further allow medication to be administered in precise, metered doses. Thus, the pharmaceutical compositions of the invention are typically suitable for intranasal administration. Further, the present invention also provides an intranasal device containing such a pharmaceutical composition.

A further preferred route of administration is transdermal administration. The present invention therefore also provides a transdermal patch containing a compound

of the invention, or a pharmaceutically acceptable salt thereof. Also preferred is sublingual administration. The present invention therefore also provides a sub-lingual tablet comprising a compound of the invention or a pharmaceutically acceptable salt thereof.

A compound of the invention is typically formulated for administration with a pharmaceutically acceptable carrier or diluent. For example, solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar coating, or film coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The compounds of the present invention are therapeutically useful in the treatment or prophylaxis of conditions involving sodium ion flux through a sensory neurone specific (SNS) channel of a sensory neurone. Said condition may be one of hypersensitivity for example resulting from a concentration of SNS channels at the

site of nerve injury or in axons following nerve injury, or may be sensitization of the neurone for example at sites of inflammation as a result of inflammatory mediators.

Said compounds of the invention are therefore most preferred for their use in the treatment or prophylaxis of any condition involving hypersensitivity or sensitization of a sensory neurone specific (SNS) channel of a sensory neurone.

Accordingly, the present invention also provides the use of a compound of formula (I) or (II), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment or prophylaxis of a condition involving sodium ion flux through a sensory neurone specific (SNS) channel of a sensory neurone, more specifically hypersensitivity of a sensory neurone or sensitisation of a sensory neurone specific (SNS) channel of a sensory neurone. Also provided is a method of treating a patient suffering from or susceptible to a condition involving sodium ion flux through a sensory neurone specific (SNS) channel of a sensory neurone more specifically hypersensitivity of a sensory neurone or sensitization of a sensory neurone specific (SNS) channel of a sensory neurone, which method comprises administering to said patient an effective amount of a compound of formula (I) or (II), or a pharmaceutically acceptable salt thereof.

The term treatment in this context is deemed to cover any effect from a cure of said condition to alleviation of any or all of the symptoms. The compounds of the invention may, where appropriate, be used prophylactically to reduce the incidence or severity of said conditions.

Specific conditions in which SNS channels are present and believed to be involved include pain namely chronic or acute pain, hypersensitivity disorders such as bladder dysfunction and bowel disorders which may or may not also have associated pain, and demyelinating diseases.

SNS sodium channels are known to mediate pain transmission. Typically, the compounds of the invention are therefore used as analgesic agents. SNS specific sodium channels have been identified as being particularly important in the transmission of pain signals. The compounds of the invention are accordingly particularly effective in alleviating pain. Typically, therefore, said medicament is for use in alleviating pain and said patient is suffering from or susceptible to pain. The compounds of the invention are effective in alleviating both chronic and acute pain.

Acute pain is generally understood to be a constellation of unpleasant sensory, perceptual and emotional experiences of certain associate autonomic (reflex) responses, and of psychological and behavioural reactions provoked by injury or disease. A discussion of acute pain can be found at Halpern (1984) *Advances in Pain Research and Therapy,* Vol.7, p.147. Tissue injury provokes a series of noxious stimuli which are transduced by nociceptors to impulses transmitted to the spinal cord and then to the upper part of the nervous system. Examples of acute pains which can be alleviated with the compounds of the invention include musculoskeletal pain, for example joint pain, lower back pain and neck pain, dental pain, post-operative pain, obstetric pain, for example labour pain, acute headache, neuralgia, myalgia, and visceral pain.

Chronic pain is generally understood to be pain that persists beyond the usual course of an acute disease or beyond a reasonable time for an injury to heal. A discussion of chronic pain can be found in the Halpern reference given above. Chronic pain is sometimes a result of persistent dysfunction of the nociceptive pain system. Examples of chronic pains which can be alleviated with the compounds of the invention include trigeminal neuralgia, post-herpetic neuralgia (a form of chronic pain accompanied by skin changes in a dermatomal distribution following damage by acute Herpes Zoster disease), diabetic neuropathy, causalgia, "phantom limb" pain, pain associated with osteoarthritis, pain associated with rheumatoid arthritis, pain associated with cancer, pain associated with HIV, neuropathic pain, migraine and other conditions associated with chronic cephalic pain, primary and secondary hyperalgesia, inflammatory pain, nociceptive pain, tabes dorsalis, spinal cord injury pain, central pain, post-herpetic pain, noncardiac chest pain, irritable bowel syndrome and pain associated with bowel disorders and dyspepsia.

Some of the chronic pains set out above, for example, trigeminal neuralgia, diabetic neuropathic pain, causalgia, phantom limb pain and central post-stroke pain, have also been classified as neurogenic pain. One non-limiting definition of neurogenic pain is pain caused by dysfunction of the peripheral or central nervous system in the absence of nociceptor stimulation by trauma or disease. The compounds of the invention can, of course, be used to alleviate or reduce the incidence of neurogenic pain.

Examples of bowel disorders which can be treated or prevented with the compounds of the invention include inflammatory bowel syndrome and inflammatory bowel disease, for example Crohn's disease and ulcerative colitis. The compounds of the

invention can also be used to alleviate pain associated with inflammatory disease or inflammatory bowel syndrome.

Examples of bladder dysfunctions which can be treated or prevented with the compounds of the invention include bladder hyper reflexia, bladder inflammation, for example interstitial cystitis, overactive (or unstable) bladder (OAB), more specifically urinary incontinence, urgency, frequency, urge incontinence, nocturia and bladder hyper reflexia. The compounds of the invention may, where appropriate, be used prophylactically to reduce the incidence of such conditions.

Examples of demyelinating diseases which can be treated or prevented with the compounds of the invention are those in which SNS channels are known to be expressed by the demyelinated neurones and which may or may not also have associated pain. A specific example of such a demyelinating disease is multiple sclerosis. The compounds of the invention can also be used to alleviate pain associated with demyelinating diseases such as multiple sclerosis.

The compounds of the present invention are also useful in the treatment or prevention of tinnitus.

A therapeutically effective amount of a compound of the invention is administered to a patient. A typical dose is from about 0.001 to 50 mg per kg of body weight, for example 0.01 to 10 mg, according to the activity of the specific compound, the age, weight and conditions of the subject to be treated, the type and severity of the disease and the frequency and route of administration. Preferably, daily dosage levels are from 5 mg to 2 g.

The following Examples illustrate the invention. They do not, however, limit the invention in any way. In this regard, it is important to understand that the particular assays used in the Examples section are designed only to provide an indication of activity in inhibiting SNS specific sodium channels. A negative result in any one particular assay is not determinative.

EXAMPLES

Example 1 (Preparation Example): 4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzaldehyde

To a stirred solution of 2-Chloro-6-fluorobenzyl chloride (Acros 20352) (0.90 ml, 7.07 mmol) in dimethylformamide (50 mL) was added 4-hydroxy-2-methoxy-benzaldehyde (Fluka 55543) (1.08 g, 7.07 mmol), potassium carbonate (1.4 g, 10.04 mmol) and the reaction was heated at 100°C for 17 hours. The reaction was concentrated *in vacuo* and the residue dissolved in dichloromethane (100 mL). The organic solution was washed (sodium hydroxide 2M), dried (magnesium sulphate) and concentrated *in vacuo* to afford the title compound as a yellow oil which crystallised on standing (1.65g, 62.2 %).

The following intermediates were prepared from the appropriate benzyl bromide and hydroxy benzaldehyde according to the method described in Example 1:

4-Benzyloxybenzaldehyde
4-Benzyloxy-3-methoxybenzaldehyde
3-(4-Formyl-phenoxymethyl)-benzonitrile
3-Methoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzaldehyde
2,6-Dimethoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzaldehyde
4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzladehyde
3-Methoxy-4-(3-methoxy-benzyloxy)-benzaldehyde
4-(2,6-Difluoro-benzyloxy)-3-methoxy-benzaldehyde
4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzaldehyde
2,6-Dimethoxy-4-(4-trifluoromethyl-benzyloxy)-benzaldehyde
4-(2-Fluoro-benzyloxy)-2,6-dimethoxy-benzaldehyde
3-Methoxy-4-(4-methoxy-benzyloxy)-benzaldehyde
4-Cyclohexylmethoxy-3-methoxy-benzaldehyde
4-Benzyloxy-3-chlorobenzaldehyde
4-Cyclohexylmethoxy-benzaldehyde

Example 2 (Preparation Example): 1-(S)-(5-Methyl-thiazol-2-yl)-ethylamine trifluoroacetate

(S)-[1-(2-Hydroxy-propylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester

To a solution of 2-(S)-tert-butoxycarbonylamino-propionic acid (5.0 g, 26.4 mmol) in dichloromethane (130 mL) was added 1-amino-2-propanol (2.38 g, 31.7 mmol), triethylamine (5.33 g, 52.8 mmol), hydroxybenzotriazole (6.05 g, 39.6 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride salt (4.91 g, 31.7 mmol) and the reaction was stirred at room temperature for 16 hours. The reaction was diluted using ethyl acetate (300 mL), washed (5% citric acid), (sat. sodium bicarbonate), (brine), dried (magnesium sulphate) and concentrated *in vacuo* to afford an orange residue. The residue was purified by flash chromatography (SiO_2, 10% methanol/ethyl acetate) to afford the title compound as a pale yellow oil (4.1 g, 63%) : 1H NMR (400 MHz, CDCl3) δ_H 1.16 (3H), 1.36 (3H), 1.43 (9H), 2.68 (1H), 3.11 (1H), 3.43 (1H), 3.91 (1H), 4.11 (1H), 5.00 (1H), 6.58 (1H).

(S)-[1-(2-Oxo-propylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester

To a solution of (S)-[1-(2-hydroxy-propylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester (0.5 g, 2.0 mmol) in dry dichloromethane (10 mL), was added 1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (1.07 g, 2.4 mmol) and the reaction stirred at room temperature for 16 hours. The reaction was diluted using ethyl acetate (30 mL), washed, (sat. sodium bicarbonate containing 2% sodium thiosulphate), (brine), dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, ethyl acetate) to afford the title compound as a clear oil (0.17 g, 35 %) : 1H NMR (400 MHz, CDCl3) δ_H 1.38 (3H), 1.44 (9H), 2.19 (3H), 4.12 (2H), 4.18 (1H), 4.94 (1H), 6.76 (1H). HPLC retention time, 2.7 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 245 (M + H).

(S)-1-(5-Methyl-thiazol-2-yl)-ethyl]-carbamic acid tert butyl ester

To a solution of (S)-[1-(2-oxo-propylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester (1.0 g, 4.1 mmol) in tetrahydrofuran (40 mL) was added 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphene-2,4-disulphide (2.5 g, 6.1 mmol) and the reaction was heated to reflux for 2 hours. After cooling, the reaction mixture was diluted using ethyl acetate (150 mL), washed (5% citric acid), (sat. sodium bicarbonate), (brine), dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 30% ethyl acetate/hexanes) to afford the title compound as a pale yellow stiff oil (0.92 g, 88%) : 1H NMR (400 MHz, CDCl3) δ_H 1.44 (9H), 1.54 (3H), 2.41 (3H), 5.01 (2H), 7.30 (1H).

1-(S)-(5-Methyl-thiazol-2-yl)-ethylamine trifluoroacetate

To a solution of (S)-1-(5-methyl-thiazol-2-yl)-ethyl]-carbamic acid tert butyl ester (0.2 g, 0.74 mmol) in dichloromethane (5 mL) was added drop wise trifluoroactetic acid (5 mL) and the reaction was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* to afford the title compound as a pale orange oil (0.12 g, 95%) : 1H NMR (400 MHz, CDCl3) δ_H 1.81 (3H), 2.53 (3H), 5.01 (2H), 7.55 (1H), 8.9 (3H).

Example 3 (Preparation Example): 1-(5-Methyl-4,5-dihydro-oxazol-2-yl)-ethylamine trifluoroactetate

(S)-[1-(5-Methyl-4,5-dihydro-oxazol-2-yl)-ethyl]-carbamic acid tert-butyl ester

A solution of (S)-[1-(2-hydroxy-propylcarbamoyl)-ethyl]-carbamic acid tert-butyl ester (0.5 g, 2.0 mmol) in dry dichloromethane (20 mL) was cooled to -70°C under an atmosphere of nitrogen. A solution of (Diethylamino) sulphur trifluoride (0.36 g, 2.2 mmol) in dichloromethane (20 mL) was added and the reaction was stirred at -78°C for 1 hour. The reaction mixture was allowed to warm to room temperature and poured gradually onto a stirred solution of saturate potassium carbonate. The reaction mixture was washed using ethyl acetate (2 x 100mL) and the organic

extracts were combined, dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified using ethyl acetate to afford the title compound as a clear oil (0.3 g, 65.8%) : 1H NMR (400 MHz, CDCl3) δ_H 1.22 (3H), 1.34 (3H), 1.58 (9H), 3.38 (1H), 3.91 (1H), 4.41 (1H), 4.7 (1H), 5.18 (1H). Mass spectrum (ES+) m/z 229 (M + H).

1-(5-Methyl-4,5-dihydro-oxazol-2-yl)-ethylamine trifluoroacetate

To a solution of (S)-[1-(5-Methyl-4,5-dihydro-oxazol-2-yl)-ethyl]-carbamic acid tert-butyl ester (0.3 g, 1.3 mmol) in dichloromethane (3 mL) was added drop wise trifluoroacetic acid (3 mL) and the reaction was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* to afford the title compound as a pale yellow oil (0.29 g, 92%)

Example 4 (Preparation Example): 1-(5-Methyl-1H-imidazol-2-yl)-ethylamine

(S)-[1-(Methoxy-methyl-carbamoyl)-ethyl]-carbamic acid tert-butyl ester

To a solution of 2-(S)-tert-butoxycarbonylamino-propionic acid (23.5 g, 124 mmol) and N-ethylmorpholine (14.2 g, 124 mmol) in dry tetrahydrofuran (500 mL) at -20°C was added isobutyl chloroformate (17 g, 124 mmol) and triethylamine (13.8 g, 136 mmol) and the reaction stirred at -20°C. A solution of *N,O*-dimethylhydroxylamine hydrochloride (Aldrich D16,370-8) (12.2 g, 124 mmol) in dimethylformamide (250 mL) was added and the reaction stirred at -20°C for a further 30 minutes. The reaction mixture was warmed to room temperature and partitioned between ethyl acetate (500 mL) and brine (500 mL) and the organic extracts collected. The organic extracts were, washed (5% citric acid), (sat. sodium bicarbonate), (brine), dried (magnesium sulphate) and evaporated to afford the title compound as a white solid (12 g, 42%) : 1H NMR (400 MHz, CDCl3) δ_H 1.12 (3H), 1.44 (9H), 3.06 (3H), 3.69 (3H), 4.37 (1H), 6.99 (1H).

(S)-[1-(5-Methyl-1H-imidazol-2-yl)-ethyl]-carbamic acid tert-butyl ester

To a solution of (S)-[1-(methoxy-methyl-carbamoyl)-ethyl]-carbamic acid tert-butyl ester (1.0 g, 4.3 mmol) in dry tetrahydrofuran (20 mL) at 0°C was added drop wise lithium aluminium hydride (1M solution in THF) (3.4 mmol) and the reaction was stirred at 0°C for 10 minutes. The reaction mixture was added drop-wise to a saturated solution of potassium hydrogen sulphate until the pH is 2. The reaction mixture was partitioned using diethyl ether (2 x 100 mL) and the organics extracts were combined, washed (brine), dried (magnesium sulphate) and concentrated *in vacuo* at 20°C. The resulting oil was dissolved in dry methanol (100 mL) and molecular sieves (4A) (5 g) were added. To the stirred solution was added pyruvic aldehyde (40% solution in H_2O) (0.78 g, 4.3 mL), ammonium acetate (3.3 g, 43 mmol) and the reaction heated to 60°C for 16 hours. The reaction was filtered and partitioned between ethyl acetate (2 x 150 mL) and 5% potassium carbonate solution (150 mL). The organic extracts were combined, washed (brine), dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 1% methanol/dichloromethane) to afford the title compound as a yellow foam (0.09g, 10%) : 1H NMR (400 MHz, CDCl3) δ_H 1.44 (9H), 1.59 (3H), 2.2 (3H), 4.74 (1H), 5.28 (1H), 6.62 (1H). Mass spectrum (ES+) m/z 229 (M + H).

Example 5: (S)-(4-Benzyloxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

To a solution of 4-benzyloxybenzaldehyde (0.23 g, 1.1 mmol) in dry methanol (10 mL) was added 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine trifluoroacetate (0.16 g, 1.1 mmol), triethylamine (0.6 g, 6 mmol) and the reaction was stirred at room temperature for 1 hour. Sodium cyanoborohydride (0.076 g, 1.2 mmol) was added and the reaction stirred at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate (50 mL) and washed (brine 100 mL), dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 2% methanol/dichloromethane) to afford the title compound as a stiff oil (0.1 g, 27%) : 1H NMR (400 MHz, CDCl3) δ_H 1.46 (3H), 2.44 (3H), 3.69 (2H), 4.06 (1H), 5.05 (2H), 6.92 (2H), 7.72-7.42 (8H).

Example 6: (S)-3-(4-{[1-(5-Methyl-thiazol)-2-yl)-ethylamino]-methyl}-phenoxymethyl)-benzonitrile

(S)-3-(4-{[1-(5-methyl-thiazol)-2-yl)-ethylamino]-methyl}-phenoxymethyl)-benzonitrile was prepared from 3-(4-formyl-phenoxymethyl)-benzonitrile and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine trifluoroacetate according to the method described in Example 5 : HPLC retention time, 4.61 min (Solvent: $MeCN/H_2O/0.05\%$ NH_4OH, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 364 (M + H).

Example 7: (S)-(4-Benzyloxy-benzyl)-[1-(5-methyl-4,5-dihydro-oxazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-benzyl)-[1-(5-methyl-4,5-dihydro-oxazol-2-yl)-ethyl]-amine was prepared from 4-benzyloxybenzaldehyde and 1-(5-Methyl-4,5-dihydro-oxazol-2-yl)-ethylamine trifluoroacetate according to the method described in Example 5 : HPLC retention time, 4.05 min (Solvent: $MeCN/H_2O/0.05\%$ NH_4OH, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 325 (M + H).

Example 8: (S)-3-(4-{[1-(5-Methyl-4,5-dihydro-oxazol-2-yl)-ethylamino]-methyl}-phenoxymethyl)-benzonitrile

(S)-3-(4-{[1-(5-Methyl-4,5-dihydro-oxazol-2-yl)-ethylamino]-methyl}-phenoxymethyl)-benzonitrile was prepared from 3-(4-formyl-phenoxymethyl)-benzonitrile and 1-(5-Methyl-4,5-dihydro-oxazol-2-yl)-ethylamine trifluoroacetate according to the method described in Example 5 : HPLC retention time, 3.83 min (Solvent: $MeCN/H_2O/0.05\%$ NH_4OH, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 351 (M + H).

Example 9: (S)-(4-Benzyloxy-benzyl)-[1-(4-methyl-1H-imidazol-2-yl)-ethyl]-amine

To a solution of (S)-[1-(5-Methyl-1H-imidazol-2-yl)-ethyl]-carbamic acid tert-butyl ester (0.09 g, 0.4 mmol) in dry dichloromethane (2 mL) was added trifluoroacetic acid (2 mL) and the reaction stirred at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo* and the residue dissolved in dry methanol (5 mL). 4-Benzyloxybenzaldehyde (0.085 g, 0.4 mmol) was added followed by triethylamine (0.12g, 1.2 mmol) and the reaction mixture was stirred at room temperature for 1 hour. Sodium cyanoborohydride (0.032 g, 0.5 mmol) was added and the reaction stirred for 16 hours at room temperature. The reaction was concentrated *in vacuo* and the residue dissolved in ethyl acetate (25 mL). The solution was washed (5% potassium carbonate), (brine), dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 5% methanol/ MTBE) to afford the title compound as a stiff oil (0.039 g, 30%) : 1H MR (400 MHz, CDCl3) δ_H 1.41 (3H), 2.24 (3H), 3.63 (2H), 4.03 (1H), 5.03 (2H), 6.63 (1H), 6.91 (2H), 7.18 (2H), 7.36-7.50 (5H). Mass spectrum (ES+) m/z 322 (M + H).

Example 10: (S)-[3-Methoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

To a solution of 3-methoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzaldehyde (0.192 g, 0.56 mmol) in dichloromethane (10 mL) was added 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt (0.1 g, 0.56 mmol), triethylamine (0.145 mL, 1.12 mmol), sodium cyanoborohydride (Acros 16855) (0.11 g, 1.68 mmol) and the reaction was stirred at room temperature for 17 hours. The reaction mixture was washed (saturated sodium bicarbonate), (brine), dried (magnesium sulphate) and concentrated *in vacuo* to afford a crude solid. The solid was purified by flash chromatography to afford the title compound as a white solid (0.06 g, 19%) : HPLC retention time, 4.54 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 469 (M + H).

Example 11: (S)-[2,6-Dimethoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]amine

(S)-[2,6-Dimethoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]amine was prepared 2,6-dimethoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.82 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 499 (M + H).

Example 12: (S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzladehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.49 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 451 (M + H).

Example 13: (S)-[3-Methoxy-4-(3-methoxy-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[3-Methoxy-4-(3-methoxy-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 3-methoxy-4-(4-methoxy-benzyloxy)-benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.15 min (Solvent:MeCN/ H_2O/ 0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 399 (M + H).

Example 14: (S)-[4-(2,6-Difluoro-benzyloxy)-3-methoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[4-(2,6-Difluoro-benzyloxy)-3-methoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 4-(2,6-difluoro-benzyloxy)-3-methoxy-benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : 1H NMR (400 MHz, CDCl3) δ_H 1.47 (3H), 2.44 (3H), 3.72 (2H), 3.84 (3H), 4.11 (1H), 5.14 (2H), 6.83 (1H), 6.89 (3H), 6.95 (1H), 7.25-7.34 (2H).
Mass spectrum (ES+) m/z 405 (M + H).

Example 15: (S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.45 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min.. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 421 (M + H).

Example 16: (S)-[2,6-Dimethoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[3-methyl-1-(5-methyl-thiazol-2-yl)-butyl]-amine

(S)-[2,6-Dimethoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[3-methyl-1-(5-methyl-thiazol-2-yl)-butyl]-amine was prepared from 2,6-Dimethoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzaldehyde and [3-methyl-1(S)-(5-methyl-thiazol-2-yl)-butyl]-amine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 3.74 min (Solvent: MeCN/H_2O/0.05% HCO_2H, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 541 (M + H).

Example 17: (S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[3-methyl-1-(5-methyl-thiazol-2-yl)-butyl]-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[3-methyl-1-(5-methyl-thiazol-2-yl)-butyl]-amine was prepared from 4-(2-chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzladehyde and [3-methyl-1(S)-(5-methyl-thiazol-2-yl)-butyl]-amine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.99 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 494 (M + H).

Example 18: (S)-[2,6-Dimethoxy-4-(4-trifluoromethyl-benzyloxy)-benzyl]-[3-methyl-1-(5-methyl-thiazol-2-yl)-butyl]-amine

(S)-[2,6-Dimethoxy-4-(4-trifluoromethyl-benzyloxy)-benzyl]-[3-methyl-1-(5-methyl-thiazol-2-yl)-butyl]-amine was prepared from 2,6-dimethoxy-4-(4-trifluoromethyl-benzyloxy)-benzaldehyde and [3-methyl-1(S)-(5-methyl-thiazol-2-yl)-butyl]-amine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 5.05 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 509 (M + H).

Example 19: (S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine was prepared from 4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzladehyde and [1(S)-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.86 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 527 (M + H).

Example 20: (S)-[2,6-Dimethoxy-4-(4-trifluoromethyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine

(S)-[2,6-Dimethoxy-4-(4-trifluoromethyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine was prepared from 2,6-dimethoxy-4-(4-trifluoromethyl-benzyloxy)-benzaldehyde and [1(S)-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.93 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 543 (M + H).

Example 21: (S)-[4-(2-Fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine

(S)-[4-(2-Fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine was prepared from 4-(2-Fluoro-benzyloxy)-2,6-dimethoxy-benzaldehyde and [1(S)-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.78 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 493 (M + H).

Example 22: (S)-(4-Benzyloxy-benzyl)-[3-methyl-1-(5-methyl-thiazol-2-yl)-butyl]-amine

(S)-(4-Benzyloxy-benzyl)-[3-methyl-1-(5-methyl-thiazol-2-yl)-butyl]-amine was prepared from 4-(benzyloxy)-benzaldehyde and [3-methyl-1(S)-(5-methyl-thiazol-2-yl)-butyl]-amine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.82 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 381 (M + H).

Example 23: (S)-(4-Benzyloxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine

(S)-(4-Benzyloxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine was prepared from 4-(benzyloxy)-benzaldehyde and [1(S)-(5-methyl-thiazol-2-yl)-2-phenyl-ethyl]-amine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.77 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 415 (M + H).

Example 24: (S)-(4-Benzyloxy-3-methoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-3-methoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 4-(benzyloxy)-3-methoxy benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.16 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 369 (M + H).

Example 25: (S)-(4-Methoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Methoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 4-methoxy benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 3.7 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 366 (M + H).

Example 26: (S)-(4-Cyclohexylmethoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-4-(Cyclohexylmethoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 4-cyclohexylmethoxy benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.93 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 345 (M + H).

Example 27: (S)-(4-Benzyloxy-3-chloro-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-3-chloro-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 4-benzyloxy-3-chlorobenzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.49 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 373 (M + H).

Example 28: (S)-(4-Benzyloxy-2-methoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-2-methoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 4-benzyloxy-2-methoxybenzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.33 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 369 (M + H).

Example 29: (S)-(4-Benzyloxy-2,6-dimethoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-2,6-dimethoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 2,6-dimethoxy-4-benzyloxybenzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in

Example 10 : HPLC retention time, 4.33 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 399 (M + H).

Example 30: (S)-(4-Benzyloxy-2-chloro-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-2-chloro-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 4-benzyloxy-2-chlorobenzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.58 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 373 (M + H).

Example 31: (S)-(4-Benzyloxy-3-ethoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-3-ethoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 4-benzyloxy-3-ethoxybenzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.33 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 383 (M + H).

Example 32: (S)-(4-Benzyloxy-3-nitro-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-3-nitro-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 4-benzyloxy-3-nitrobenzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.24 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 384 (M + H).

Example 33: (S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-(5-methyl-isoxazol-3-ylmethyl)-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-(5-methyl-isoxazol-3-ylmethyl)-amine was prepared from 4-(2-chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzaldehyde and C-(5-methyl-isoxazol-3-yl)-methylamine according to the method described in Example 10 : 1H NMR (400 MHz, $CDCl_3$) δ_H 2.38 (3H), 3.78 (10H), 5.19 (2H), 6.00 (1H), 6.23 (2H), 7.04 (1H), 7.20-7.35 (2H). Mass spectrum (ES+) m/z 421 (M + H).

Example 34: (S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-(1-methyl-1H-pyrrol-2-ylmethyl)-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-(1-methyl-1H-pyrrol-2-ylmethyl)-amine was prepared from 4-(2-chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzaldehyde and C-(1-methyl-1H-pyrrol-2-yl)-methylamine according to the method described in Example 10 : HPLC retention time, 4.72 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 419 (M + H).

Example 35: (S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-thiophen-3-ylmethyl-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-thiophen-3-ylmethyl-amine was prepared from 4-(2-chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzaldehyde and C-thiophen-3-yl-methylamine according to the method described in Example 10 : HPLC retention time, 4.85 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 422 (M + H).

Example 36: (S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-(1,3,5-trimethyl-1H-pyrazol-4-ylmethyl)-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-(1,3,5-trimethyl-1H-pyrazol-4-ylmethyl)-amine was prepared from 4-(2-chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzaldehyde and C-(1,3,4-trimethyl-1H-pyrazole-4-yl)-methylamine according to the method described in Example 10 : HPLC retention time, 4.19 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 487 (M + CH_2CN).

Example 37: (S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-thiophen-2-ylmethyl-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-thiophen-2-ylmethyl-amine was prepared from 4-(2-chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzaldehyde and C-thiophen-2-yl-methylamine according to the method described in Example 10 : HPLC retention time, 4.71 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 422 (M + H).

Example 38: (S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-(3-methyl-thiophen-2-ylmethyl)-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-(3-methyl-thiophen-2-ylmethyl)-amine was prepared from 4-(2-chloro-6-fluoro-benzyloxy)-2,6-dimethoxy-benzaldehyde and C-(3-methyl-thiophen-2-yl)-methylamine according to the method described in Example 10 : HPLC retention time, 4.77 min (Solvent: MeCN/H_2O/ 0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 436 (M + H).

Example 39: (S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-[1-methyl-1H-pyrrol-2-ylmethyl)-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-[1-methyl-1H-pyrrol-2-ylmethyl)-amine was prepared from 4-(2-chloro-6-fluoro-benzyloxy)-2,-methoxy-benzaldehyde and C-(1-methyl-1H-pyrrol-2-yl)-methylamine according to the method described in Example 10 : 1H NMR (400 MHz, $CDCl_3$) δ_H 3.62 (3H), 3.71 (2H), 3.75-3.80 (5H), 5.18 (2H), 6.03 (2H), 6.50-6.64 (3H), 7.04 (1H), 7.18 (1H), 7.22-7.34 (2H). Mass spectrum (ES+) m/z 389 (M + H).

Example 40: (S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-thiophen-3-ylmethyl-amine

S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-thiophen-3-ylmethyl-amine was prepared from 4-(2-chloro-6-fluoro-benzyloxy)-2,-methoxy-benzaldehyde and C-thiophen-3-yl-methylamine according to the method described in Example 10 : HPLC retention time, 4.60 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 392 (M + H).

Example 41: (S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-(5-methyl-isoxazol-3-ylmethyl)-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-(5-methyl-isoxazol-3-ylmethyl)-amine was prepared from 4-(2-chloro-6-fluoro-benzyloxy)-2,-methoxy-benzaldehyde and C-(5-methyl-isoxazol-3-yl)-methylamine according to the method described in Example 10 : HPLC retention time, 4.17 min (Solvent: MeCN/H_2O/ 0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 391 (M + H).

Example 42: (S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-(3-methyl-thiophen-2-ylmethyl)-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-2-methoxy-benzyl]-(3-methyl-thiophen-2-ylmethyl)-amine was prepared from 4-(2-chloro-6-fluoro-benzyloxy)-2,-methoxy-benzaldehyde and C-(3-methyl-thiophen-2-yl)-methylamine according to the method described in Example 10 : 1H NMR (400 MHz, $CDCl_3$) δ_H 2.17 (3H), 3.80-3.90 (7H), 5.21 (2H), 6.54-6.64 (2H), 6.82 (1H), 7.10-7.20 (3H), 7.24-7.36 (2H). Mass spectrum (ES+) m/z 406 (M + H).

Example 43: (S)-[4-(2,6-Difluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[4-(2,6-Difluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 4-(2,6-difluoro-benzyloxy)-2,6-dimethoxy-benzaldehyde and 1-(5-methyl-thiazol-2-yl)-ethylamine according to the method described in Example 10 : HPLC retention time, 4.34 min (Solvent: MeCN/H_2O/ 0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 435 (M + H).

Example 44: (S)-(4-Benzyloxy-3,5-dimethoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-3,5-dimethoxy-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 4-benzyloxy-3,5-dimethoxy-benzaldehyde and 1-(5-methyl-thiazol-2-yl)-ethylamine according to the method described in Example 10 : HPLC retention time, 4.20 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 399 (M + H).

Example 45: (S)-[2,6-Dimethoxy-4-(2,4,6-trifluoro-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[2,6-Dimethoxy-4-(2,4,6-trifluoro-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 2,6-dimethoxy-4-(2,4,6-trifluoro-

benzyloxy)benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.36 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 453 (M + H).

Example 46: (S)-(4-Benzyloxy-3-methyl-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-(4-Benzyloxy-3-methyl-benzyl)-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 3-methyl-4-benzyloxy-benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.63 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 353 (M + H).

Example 47: (S)-2-Benzyloxy-5-{[1-(5-methyl-thiazol-2-yl)-ethylamino]-methyl}-phenylamine

(S)-2-Benzyloxy-5-{[1-(5-methyl-thiazol-2-yl)-ethylamino]-methyl}-phenylamine was prepared from 3-amino-4-benzyloxy-benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 3.95 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 354 (M + H).

Example 48 : (S)-[4-(4-Fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[4-(4-Fluoro-benzyloxy)-2,6-dimethoxy-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 2,6-dimethoxy-4-(4-fluorobenzyloxy)-benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.37 min (Solvent:

MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 417 (M + H).

Example 49 : (S)- [3-Chloro-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[3-Chloro-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 3-chloro-4-(4-trifluorothiomethoxybenzyloxy)-benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.62 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 472, 474 (M + M+2H).

Example 50 : (S)-[3-Chloro-4-(2-chloro-6-fluoro-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[3-Chloro-4-(2-chloro-6-fluoro-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 3-chloro-4-(2-chloro-6-fluorobenzyloxy)-benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.56 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 425, 427 (M + M+2H).

Example 51 : (S)-[1-(5-Methyl-thiazol-2-yl)-ethyl]-[3-nitro-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-amine

(S)-[1-(5-Methyl-thiazol-2-yl)-ethyl]-[3-nitro-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-amine was prepared from 3-nitro-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC

retention time, 4.72 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 484 (M + H).

Example 52 : (S)-[2-Chloro-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[2-Chloro-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 2-chloro-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.9 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 472,474 (M, M+2H).

Example 53 : (S)-[2-Chloro-4-(2-chloro-6-fluoro-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[2-Chloro-4-(2-chloro-6-fluoro-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 2-chloro-4-(2-chloro-6-fluorobenzyloxy)-benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.74 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 425,427 (M, M+2H).

Example 54 : (S)-[4-(2-Chloro-6-fluoro-benzyloxy)-3-nitro-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[4-(2-Chloro-6-fluoro-benzyloxy)-3-nitro-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 3-nitro-4-(2-chloro-6-fluorobenzyloxy)-benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.38 min

(Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 435,437 (M, M+2H).

Example 55 : (S)-[2-Methoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine

(S)-[2-Methoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzyl]-[1-(5-methyl-thiazol-2-yl)-ethyl]-amine was prepared from 3-methoxy-4-(4-trifluoromethylsulfanyl-benzyloxy)-benzaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 4.87 min (Solvent: MeCN/H_2O/0.05% NH_4OH, 5-95% gradient H_2O – 6 min. Column: Xterra 50 x 4.60 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 469 (M+).

Example 56: N*3*-(4-Phenoxy-benzyl)-1H-[1,2,4]triazole-3,5-diamine

1-Cyano-3-(4-phenoxy-benzyl)-2-phenyl-isourea

To a solution of 4-phenoxybenzylamine (Transworld P1284) (0.2 g, 1.1 mmol) in isopropanol was added diphenyl cyanocarbonimidate (0.25 g, 1.1 mmol) and the reaction stirred at ambient temperature for 1 hour. The precipitate was collected by filtration, washed (propan-2-ol), dried (vacuum) to afford the title compound as a white crystalline solid.

*N*3*-(4-Phenoxy-benzyl)-1H-[1,2,4]triazole-3,5-diamine*

To a solution of 1-Cyano-3-(4-phenoxy-benzyl)-2-phenyl-isourea (0.05 g, 0.15 mmol) in propan-2-ol (5 mL) was added hydrazine hydrate (0.016 g, 0.3 mmol) and the reaction was heated to reflux for 2 hours. The reaction was allowed to cool and concentrated *in vacuo* to afford a crude solid. The solid was recrystallised from isopropanol to afford the title compound as a white crystalline solid : Mass Spectrum (ES+) m/z 282 (M + H).

Example 57: (4-Phenyl-butyl)-(5-phenyl-2H-[1,2,3]triazol-4-ylmethyl)-amine

5-phenyl-2H-[1,2,3]-triazole-4-carbaldehyde

To a stirred solution of phenylacetylene (Aldrich 11,770-6) (5.1g, 50 mmol) in anhydrous tetrahydrofuran (125 mL) at - 40°C under nitrogen was added drop wise over c.a 2 min nButyl lithium (Aldrich 18,617-1) (31.3 mL, 50 mmol) whilst maintaining the temperature (internal) between -35°C to - 40°C with external cooling. To this solution was added anhydrous dimethyl formamide (7.75 mL) and the reaction mixture allowed to warm to room temperature, stirred for 0.5h and quenched by pouring into a rapidly stirred biphasic solution of 10% potassium dihydrogen phosphate (270 mL) and methyl tert-butyl ether (250 mL), cooled to c.a. -5°C. The layers were separated and the aqueous layer extracted with methyl tert-butyl ether (100 mL). The combined organic layers were washed with water (2 x 200 mL), dried (magnesium sulphate) and evaporated to dryness *in vacuo*. The residue was purified by flash column chromatography to give 6.1g of a pale yellow oil. A solution of this oil (3.1g in dimethyl sulphoxide (17.5 mL) was added to a vigorously stirred solution of sodium azide (Aldrich 19,993-1) (1.79g, 27.5 mmol) in dimethyl sulphoxide (55 mL) over c.a. 10 min whilst maintaining the temperature (internal) between 20 to 25°C. The reaction mixture was stirred for a further 0.5h and then quenched by pouring into a rapidly stirred biphasic solution of 15% potassium dihydrogen phosphate (150 mL) and methyl tert-butyl ether (160 mL). The organic layer was separated and washed with water (2 x 100 mL). The aqueous layers were re-extracted with methyl tert-butyl ether (100 mL) and the combined organic layers dried (magnesium sulphate) and evaporated *in vacuo* to afford the title compound as an off white solid (3.1g, 65%) : ^{1}H NMR (400MHz, $CDCl_3$) δH 7.46-7.59 (3H), 7.66-7.89 (2H), 10.14 (1H), 16.08 (1H,).

(4-Phenyl-butyl)-(5-phenyl-2H-[1,2,3]triazol-4-ylmethyl)-amine

To a solution of 5-phenyl-2H-[1,2,3]-triazole-4-carbaldehyde (0.250g, 1.4 mmol) in anhydrous methanol (5 mL) was added as solution of 4-phenylbutylamine (Aldrich

14,539-4) in anhydrous methanol (5mL), followed by sodium cyanoborohydride (Aldrich 15,615-9) (0.108g, 1.73 mmol) and the reaction stirred at ambient temperature for 17 hours. The reaction was concentrated *in vacuo* and the residue re-dissolved in ethyl acetate (25 mL), washed with distilled water (10 mL), dried (magnesium sulphate) and concentrated *in vacuo*. The residue was purified by preparative HPLC (Solvent: MeCN/H2O/0.05% HCOOH, 5-95% gradient H2O-6min. Column: Phenomenex 50 x 3.00 i.d., C18 reverse phase. Flow rate: 15mL/min.) to afford the title compound as a white solid (0.042g, 11%) : 1H NMR (400MHz, CDCl3) δ_H 1.51 (4H), 2.49 (2H), 2.71(2H), 4.05(2H), 7.15-7.76 (10H), 8.71(1H) : Mass Spectrum (ES+) m/z 307 (M + H).

Example 58: 4-(4-Fluoro-phenoxy)-N-(4-methyl-thiazol-2-yl)-benzenesulfonamide

4-(4-Fluorophenoxy)-benzenesulfonyl chloride.

To a stirred solution of 4-Fluorodiphenylether (Avocado, 21380) (2.35g, 12.5mmol) in dichloromethane (20mL) at -5°C was added drop wise, chlorosulfonic acid (Acros, 30449) (3.64g, 31.25mmol, 2.1ml) maintaining the temperature (internal) between 0 and 5°C. The reaction mixture was stirred at 10°C for 30mins and was quenched onto ice/H_2O (100g) with rapid stirring. The emulsion was filtered through celite and the filtrate extracted with dichloromethane (3 x 30 mL). The combined extracts were washed (brine, 2 x 50 mL), dried (magnesium sulphate) and evaporated to dryness *in vacuo* to afford the title compound as a white solid (2 g, 56%): ^{1}H NMR (400MHz, $CDCl_3$) δ_H 7.05-7.15 (6H, m), 7.95-8.00 (2H, q); LC-MS [ES-] m/z 267 (M-19)

4-(4-Fluoro-phenoxy)-N-(4-methyl-thiazol-2-yl)-benzenesulfonamide

To a solution of 2-amino-4-methylthiazole (Aldrich, A6,600-6) (0.09g, 0.75mmol) in pyridine (10 mL) was added portion-wise solid 4-(4-fluorophenoxy)-benzenesulfonyl chloride at room temperature. The reaction mixture was stirred for two hours, diluted with H_2O (25 mL) and portioned with ethyl acetate (15 mL). The organic extracts were washed (H_2O), dried (magnesium sulphate) and concentrated *in vacuo*

to afford a crude residue. flash chromatography (SiO_2 2% methanol/dichloromethane), to afford the title compound as a pink crystalline solid (0.13g, 45%) : ^{1}H NMR (400 MHz CD_3OD)δ_H 2.10 (3H),6.25 (1H), 7.0 (2H), 7.05-7.20 (4H), 7.80-7.90 (2H), Mass spectrum (ES+) m/z 365 (M+H)

Example 59: 4-(4-Fluoro-phenoxy)-N-(2-piperidin-1-yl-ethyl)-benzenesulfonamide

To a solution of 1-(2-aminoethyl)-piperidine (Aldrich 14,166-6) (0.40g, 3.12 mmol) and triethylamine (Acros 15791) (0.34g, 3.40mmol) in dichloromethane (25 mL) was added portion-wise 4-(4-fluoro-phenoxy)-benzenesulfonyl chloride (0.98g, 3.4mmol) at room temperature. The reaction mixture was stirred for 17 hours, diluted with H_2O (25 mL) and the organic layer collected. The aqueous layer was extracted with dichloromethane (2 x 15 mL) and the combined organic extracts were dried (magnesium sulphate) and concentrated in vacuo to afford a crude residue. The residue was purified by flash chromatography (SiO_2 2%methanol/dichloromethane), to afford the title compound as a white crystalline solid (1.0g, 85%): ^{1}H NMR (400 MHz CD_3OD)δ_H 1.40 (2H), 1.50-1.60 (4H), 2.30-2.45 (6H), 2.95-3.0 (2H), 7.0-7.2 (6H) 7.80-7.85 (2H). Mass spectrum (ES+) m/z 379 (M + H)

Example 60: 4-(4-Fluoro-phenoxy)-N-(5-methylsulphanyl-[1,3,4]-thiadiazol-2-yl)-benzenesulfonamide

4-(4-Fluoro-phenoxy)-N-(5-methylsulphanyl-[1,3,4]-thiadiazol-2-yl)-benzenesulfonamide was prepared from 4-(4-fluoro-phenoxy)-benzenesulfonyl chloride (0.23g, 0.79mmol) and 2-amino-5-(methylthio)-1,3,4 thiadiazole (Aldrich, 49,421-6) (0.11g, 0.75mmol) according to the method described in example 4 with the following modification. The crude reaction mixture was purified by preparative HPLC to afford the title compound as a white crystalline solid (0.04g, 14%): HPLC retention time, 3.83min (Solvent: MeCN/H_2O/0.05% HCOOH, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 3.00 i.d., C18 reverse phase. Flow rate: 1.5ml/min.): ^{1}H NMR (400 MHz $(CD_3)_2SO$) δ_H 2.65 (3H),7.05-7.10 (2H), 7.15-7.25 (2H), 7.70-7.35. (2H), 7.75-7.80 (2H). Mass spectrum (ES+) m/z 398 (M + H).

Example 61: 1-[4-(4-Fluorophenoxy)-benzenesulfonyl]-piperidine-3-carboxylic acid amide

To a solution of nipecotamide (Aldrich, N810-5) (96mg, 0.75mmol) in pyridine (2 mL) was added portion-wise solid 4-(4-fluorophenoxy)-benzenesulfonyl chloride (226mg, 0.788mmol) at room temperature. The reaction mixture was stirred for 2 hours, diluted with H_2O (10 mL) and portioned with ethyl acetate (3 x 10 mL). The organic extracts were washed (water), dried (magnesium sulphate) and concentrated *in vacuo* to afford a crude residue. The residue was purified by preparative HPLC [Retention time, 3.45min (Solvent: MeCN/H_2O/0.05% HCOOH, 5-95% gradient H_2O 6min. Column: Phenomenex 50 x 3.00 i.d., C18 reverse phase. Flow rate: 1.5ml/min.)] to afford the title compound as a pale yellow crystalline solid (23 mg, 8%): ^{1}H NMR (400MHz, DMSO) δ_H 7.68 (2H, d), 7.37 (1H, br s), 7.2-7.32 (4H, m), 6.87 (1H, br s), 3.5-3.6 (2H, m), 2.3-2.4 (1H, m), 2.1-2.18 (1H, m), 1.7 (2H, m), 1.4 (1H, m), 1.2, (2H, m); LC-MS [ES+] m/z 379 (M+H)

Example 62: (4-Phenoxy-benzyl)-(5-phenyl-2H-[1,2,3]traizole-4ylmethyl)amine

(4-Phenoxy-benzyl)-5-phenyl-2H-[1,2,3]traizole-4ylmethyl)amine was prepared from 5-phenyl-2H-[1,2,3]-triazole-4-carbaldehyde and 4-phenoxy-benzylamine (Fluorochem P1284) (0.432 g, 2.16 mmol) according to the method described in example 2 with the following modification. The residue was purified by flash column chromatography to afford the title compound as a white solid (0.143 g, 18.5 %) : HPLC retention time 2.64 min ((Solvent: MeCN/H2O/0.05% NH3, 5-95% gradient H2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 357 (M+H).

Example 63: N-(2-Diethylamino-ethyl)-4-(4-fluoro-phenoxy)-benzenesulfonamide

To a solution of *N,N*- diethylethylenediamine (Aldrich 112720) (0.038g, 0.325 mmol) in pyridine (3 mL) was added 4-(4-Fluoro-phenoxy)-benzenesulfonyl chloride (0.098 g, 0.342 mmol) and the reaction was stirred at room temperature for 17 hour. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate

(3 x 15 mL). The organic layers were combined and washed (brine), dried (magnesium sulphate) and concentrated *in vacuo* to afford a crude oil. The oil was purified by flash column chromatography to afford the title compound as a pale yellow oil (0.007g, 6%). 1H NMR (400 MHz, $CDCl_3$) δ_H 0.08-0.95 (6H), 2.37 (4H), 2.47 (2H), 2.93 (2H), 6.97-7.13 (6H), 7.80 (2H) : Mass spectrum (ES+) m/z 367 (M + H).

Example 64: 3-[4-(2,6-Difluoro-benzyloxy)-3-methoxy-phenyl]-1H-pyrazole

1-[4-(2,6-Difluoro-benzyloxy)-3-methoxy-phenyl]-ethanone

To a stirred solution of 1-(4-hydroxy-3-methoxy-phenyl)-ethanone (1.2 g, 7.07 mmol) in dimethylformamide (50 mL) was added 2,6-difluorobenzyl bromide (Aldrich 26,443-1) (1.5 g, 7.07 mmol), potassium carbonate (1.4 g, 10.04 mmol) and the reaction was heated at 100°C for 17 hours. The reaction was concentrated *in vacuo* and the residue dissolved in dichloromethane (100 mL). The organic solution was washed (sodium hydroxide 2M), dried (magnesium sulphate) and concentrated *in vacuo* to afford the title compound as a white crystalline solid (1.3g, 62 %) : HPLC retention time, 3.83 min (Solvent: MeCN/H_2O/0.05% HCO_2H, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 293 (M + H).

1-[4-(2,6-Difluoro-benzyloxy)-3-methoxy-phenyl]-3-dimethylamino-propenone

To a solution of 1-[4-(2,6-Difluoro-benzyloxy)-3-methoxy-phenyl]-ethanone (1.3 g, 4.3 mmol) in dimethyl formamide (20 mL) was added N,N-dimethylformamide dimethylacetal (0.52 g, 4.4 mmol) and the reaction was heated at reflux for 24 hours. The reaction mixture was allowed to cool, diluted with water (50 mL) and partitioned with ethyl acetate (20 mL). The aqueous extract was washed with ethyl acetate (2 x 20 mL) and the organic extracts combined, dried (magnesium sulphate) and concentrated *in vacuo* to afford the title compound as a yellow oil (1.4 g, 92%) : HPLC retention time, 3.65, 3.84 (*E/Z*) min (Solvent: MeCN/H_2O/0.05% HCO_2H, 5-

95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 348 (M + H).

3-[4-(2,6-Difluoro-benzyloxy)-3-methoxy-phenyl]-1H-pyrazole

To a solution of 1-[4-(2,6-Difluoro-benzyloxy)-3-methoxy-phenyl]-3-dimethylamino-propenone (1.4 g, 4 mmol) in ethanol (10 mL) was added hydrazine hydrate (0.8 g, 16 mmol) and the reaction was stirred at reflux for 16 hours. The reaction was allowed to cool, diluted with water (100mL) and partitioned with ethyl acetate (50 mL). The aqueous extracts was washed with ethyl acetate (2 x 50 mL) and the organic extracts were combined, dried (magnesium sulphate) and concentrated *in vacuo* to afford a crude solid. The solid was purified by flash chromatography (SiO_2, 30% ethyl acetate/hexanes) to afford the title compound as a white crystalline solid : HPLC retention time, 3.69 min (Solvent: MeCN/H_2O/0.05% HCO_2H, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 317 (M + H).

Example 65 : 3-[4-(2,6-Difluoro-benzyloxy)-3-methoxy-phenyl]-pyrazole-1-carboxylic acid amide

To a solution of 3-[4-(2,6-Difluoro-benzyloxy)-3-methoxy-phenyl]-1H-pyrazole (0.21 g, 0.73 mmol) in glacial acetic acid (3 mL containing 0.05 mL H_2O) was added a solution of sodium cyanate (Aldrich, 18,508-6) (0.06 g, 0.73 mmol) in water (0.05 mL) and the reaction was stirred at ambient temperature for 16 hours. The reaction was diluted with water (20 mL) and partitioned with ethyl acetate (20 mL). The aqueous extract was washed with ethyl acetate (2 x 20 mL) and the organic extracts combined, dried (magnesium sulphate) and evaporated to afford pale yellow solid. The crude solid was purified by flash chromatography (SiO_2) to afford the title compound as a white crystalline solid : HPLC retention time, 3.89 min (Solvent: MeCN/H_2O/0.05% HCO_2H, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 330 (M + H).

Example 66: 3-[4-(2,6-Difluoro-benzyloxy)-phenyl]-pyrazole-1-carboxylic acid amide

1-[4-(2,6-Difluoro-benzyloxy)-phenyl]-ethanone

To a stirred solution of 4'-hydroxyacetophenone (Aldrich 27,856-4) (0.95 g, 7.07 mmol) in dimethylformamide (50 mL) was added 2,6-difluorobenzyl bromide (Aldrich 26,443-1) (1.5 g, 7.07 mmol), potassium carbonate (1.4 g, 10.04 mmol) and the reaction was heated at 100°C for 17 hours. The reaction was concentrated *in vacuo* and the residue dissolved in dichloromethane (100 mL). The organic solution was washed (sodium hydroxide 2M), dried (magnesium sulphate) and concentrated *in vacuo* to afford the title compound as a white crystalline solid (1.1g, 54 %) : HPLC retention time, 3.92 min (Solvent: MeCN/H_2O/0.05% HCO_2H, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 263 (M + H).

1-[4-(2,6-Difluoro-benzyloxy)-phenyl]-3-dimethylamino-propenone

To a solution of 1-[4-(2,6-Difluoro-benzyloxy)-phenyl]-ethanone (1.1 g, 4.3 mmol) in dimethyl formamide (20 mL) was added N,N-dimethylformamide dimethylacetal (0.52 g, 4.4 mmol) and the reaction was heated at reflux for 24 hours. The reaction mixture was allowed to cool, diluted with water (50 mL) and partitioned with ethyl acetate (20 mL). The aqueous extract was washed with ethyl acetate (2 x 20 mL) and the organic extracts combined, dried (magnesium sulphate) and concentrated *in vacuo* to afford the title compound as a yellow oil (1.3 g, 95%) : HPLC retention time, 3.73, 3.93 (*E/Z*) min (Solvent: MeCN/H_2O/0.05% HCO_2H, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 318 (M + H).

3-[4-(2,6-Difluoro-benzyloxy)-phenyl]-1H-pyrazole

To a solution of 1-[4-(2,6-Difluoro-benzyloxy)-phenyl]-3-dimethylamino-propenone (1.3 g, 4 mmol) in ethanol (10 mL) was added hydrazine hydrate (0.8 g, 16 mmol)

and the reaction was stirred at reflux for 16 hours. The reaction was allowed to cool, diluted with water (100mL) and partitioned with ethyl acetate (50 mL). The aqueous extracts was washed with ethyl acetate (2 x 50 mL) and the organic extracts were combined, dried (magnesium sulphate) and concentrated *in vacuo* to afford a crude solid. The solid was purified by flash chromatography (SiO_2, 30% ethyl acetate/hexanes) to afford the title compound as a white crystalline solid : HPLC retention time, 3.69 min (Solvent: MeCN/H_2O/0.05% HCO_2H, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 287 (M + H).

3-[4-(2,6-Difluoro-benzyloxy) -phenyl]-pyrazole-carboxylic acid amide

3-[4-(2,6-Difluoro-benzyloxy)-phenyl]-1H-pyrazole-1-carboxamide was prepared from 3-[4-(2,6-difluoro-benzyloxy)phenyl]-1H-pyrazole and sodium cyanate (Aldrich, 18,508-6) according to the method described in Example 10 : HPLC retention time, 3.80 min (Solvent: MeCN/H_2O/0.05% HCO_2H, 5-95% gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 360 (M + H).

Example 67 : (S)-[1-(5-Methyl-thiazol-2-yl)-ethyl]-(2-phenyl-benzofuran-5-ylmethyl)-amine

4-(1-Phenyl-ethylideneamineooxy)-benzaldehyde

To a stirred solution of acetophenone (Aldrich A1,070-1) (17.06g, 142.0 mmol) in anhydrous ethanol (200 mL) was added hydroxylamine hydrochloride (Aldrich 25,558-0) (15.3g, 222.0 mmol), sodium acetate (Aldrich 11,019-1) (18.4g, 224.0 mmol) and water (100 mL). The reaction was heated at reflux for 3 hours and then cooled to room temperature. The ethanol was removed *in vacuo* and the aqueous residue quenched with 0.5M hydrochloric acid (100 mL) and extracted with diethyl ether. The combined organic layers were extracted with water (100 mL), brine (100 mL), dried (magnesium sulphate) and the solvent removed *in vacuo* to give a red oil which was purified by flash column chromatography to give a white solid (18.1 g).

This was dissolved in tetrahydrofuran (1.5 L) and sodium hydride (Aldrich 45,291-2) (60% dispersion in mineral oil, 6.43g, 161 mmol) was added portion-wise. A solution of 4-fluorobenzaldehyde (Aldrich 12,837-6) (16.6 g, 134 mmol) in dimethyl sulphoxide (100 mL) was added over 0.5 h and the reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was quenched by the addition of 200 mL of ice-cold 10% hydrochloric acid and extracted with diethyl ether (3 x 250 mL). The combined organic layers were extracted with water (100 mL), brine (100 mL), dried (sodium sulphate) and the solvent removed *in vacuo* to give a red oil which was purified by flash column chromatography to give a pale yellow oil which was crystallised from diethyl ether/isohexane to give the title compound as a pale yellow solid (12.0g, 36%) : HPLC retention time 4.09 min (Solvent: MeCN/H20/0.05% HCOOH, 5-95% gradient H_2O-6 min Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5ml/min.). Mass Spectrum (ES+) m/z 240 (M +H)

2-Phenyl-benzofuran-5-carbaldehyde

A solution of 4-(1-Phenyl-ethylideneamineooxy)-benzaldehyde (5.5 g, 2.46 mmol) in 1M hydrogen chloride in acetic acid (Aldrich 30,417-4) (70 mL) was stirred at 100°C for 17 hours. The reaction mixture was cooled to room temperature, poured onto crushed ice (100 g), and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were extracted with sodium bicarbonate (sat) (4 x 100 mL), water (100 mL), brine (100 mL), dried (magnesium sulphate) and concentrated *in vacuo* to give a red oil which was purified by flash column chromatography to give the title compound as an off white solid (2.01g, 39%) : ^{1}H NMR (400MHz, $CDCl_3$) δH 7.01 (1H), 7.35-7.60 (4H), 7.76-7.85 (3H), 8.07 (1H), 10.09 (1H)

(S)-[1-(5-Methyl-thiazol-2-yl)-ethyl]-(2-phenyl-benzofuran-5-ylmethyl)-amine

(S)-[1-(5-Methyl-thiazol-2-yl)-ethyl]-(2-phenyl-benzofuran-5-ylmethyl)-amine was prepared from 2-phenyl-benzofuran-5-carbaldehyde and 1-(S)-(5-methyl-thiazol-2-yl)-ethylamine hydrochloride salt according to the method described in Example 10 : HPLC retention time, 3.94 min (Solvent: MeCN/H_2O/0.05% HCO_2H, 5-95%

gradient H_2O – 6 min. Column: Phenomenex 50 x 3.00 mm i.d., C18 reverse phase. Flow rate: 1.5 ml/min.). Mass spectrum (ES+) m/z 349 (M + H).

Biological Screening

Inhibition of Human $Na_V1.8$ stably expressed in SH-SY-5Y cells

A SH-SY-5Y neuroblastoma cell line stably expressing the human $Na_V1.8$ ($hNa_V1.8$) ion channel was constructed. This cell line has been used to develop a medium to high throughput assay for determining the ability of test compounds to inhibit membrane depolarisation mediated via the $hNa_V1.8$ channel.

SH-SY-5Y $hNa_V1.8$ are grown in adherent monolayer culture using 50:50 Ham's F-12 / EMEM tissue culture medium supplemented with 15% (v/v) foetal bovine serum; 2mM L-glutamine, 1% NEAA and 600$\mu g.ml^{-1}$ Geneticin sulphate. Cells are removed from the tissue culture flask using trypsin/EDTA and re-plated into black walled, clear bottom 96-well assay plates at 50,000$cells.well^{-1}$ 24 hours prior to assay.

On the day of assay the cell assay plates are washed to remove cell culture medium using a sodium free assay buffer (145mM tetramethyl ammonium chloride; 2mM calcium chloride; 0.8mM magnesium chloride hexahydrate; 10mM HEPES; 10mM glucose; 5mM potassium chloride, pH 7.4). Fluorescent membrane potential dye solution (FLIPR™ membrane potential dye, Molecular Devices Corporation), containing 10μM of a pyrethroid to prevent channel inactivation and 250nM tetrodotoxin (TTX) to reduce interference from TTX-sensitive sodium channels present in the cell line. Test compound, initially dissolved in dimethyl sulfoxide but further diluted in sodium free buffer, is added to achieve the final test concentration range of 100μM – 0.05μM.

Cell plates are incubated for 30 minutes at room temperature to allow equilibration of dye and test compound. Plates are then transferred to a fluorescence plate reader for fluorescence measurement using an excitation wavelength of 530nm whilst measuring fluorescence emission at 565nm. Baseline fluorescence levels are first determined before the addition of a sodium containing buffer (220mM sodium chloride; 2mM calcium chloride; 0.8mM magnesium chloride hexahydrate; 10mM HEPES; 10mM glucose; 5mM potassium chloride. pH 7.4) to cause membrane

depolarisation in those cells where channel block has not been effected (final sodium concentration = 72.5mM). Membrane depolarisation is registered by an increase in fluorescence emission at 565nm.

The change in fluorescence seen in each test well upon the addition of sodium containing buffer is calculated relative to the baseline fluorescence for that well. This figure is then used for calculating the IC_{50} for each test compound. The results are set out in the Table below.

RESULTS

TABLE 1

Compound	IC_{50}
Example 5	3.83
Example 6	3.59
Example 9	2.43
Example 10	3.11
Example 11	0.42
Example 12	0.29
Example 13	4.61
Example 14	7.10
Example 15	3.35
Example 16	2.75
Example 33	0.57
Example 34	0.38
Example 35	0.29
Example 37	0.29
Example 38	0.26
Example 17	1.12
Example 39	0.61
Example 40	0.46
Example 41	0.99

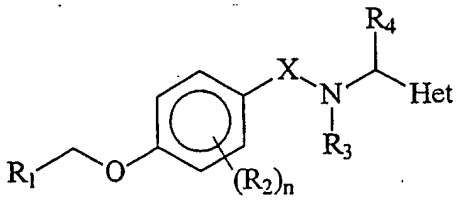
Example 18	1.06
Example 19	1.33
Example 20	0.81
Example 21	1.27
Example 22	2.68
Example 23	4.82
Example 24	7.48
Example 25	32.75
Example 26	1.69
Example 27	5.78
Example 28	2.33
Example 29	1.18
Example 30	3.56
Example 31	5.22
Example 32	3.15
Example 43	0.40
Example 44	5.57
Example 42	0.27
Example 45	0.93
Example 46	1.89
Example 47	5.60
Example 48	0.91
Example 49	7.00
Example 50	6.14
Example 51	6.40
Example 52	6.47
Example 53	3.52
Example 54	2.76
Example 55	1.17

TABLE 2

Compound	IC_{50}
Example 56	6.79
Example 57	1.01
Example 58	18.39
Example 59	2.43
Example 60	0.93
Example 61	5.59
Example 62	3.11
Example 63	16.55
Example 64	25.00
Example 65	33.27
Example 66	25.41

CLAIMS

1. Use of a compound of formula (II), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment or prevention of a condition where SNS sodium channels are involved in the underlying mechanism of the disease or in producing symptoms that can be treated separately,



(II)

wherein:

- R_1 represents hydrogen, C_1-C_6 alkyl, C_6-C_{10} aryl, a 5- to 10- membered heteroaryl group, a 5- to 10- membered heterocyclyl group or a C_3-C_6 carbocyclyl group;
- each R_2 is the same or different and represents C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy, C_1-C_6 alkythio, hydroxy, nitro, cyano, amino, (C_1-C_6 alkyl)amino or di-(C_1-C_6 alkyl)amino;
- R_3 represents hydrogen, C_1-C_6 alkyl, or together with R_4 represents a C_2-C_4 alkylene group;
- R_4 represents hydrogen, C_1-C_6 alkyl, C_6-C_{10} aryl, C_3-C_6 carbocyclyl, a 5- to 10- membered heteroaryl group, a 5- to 10- membered heterocyclyl group, -(C_1-C_6 alkyl)-aryl, -(C_1-C_6 alkyl)-(C_3-C_6 carbocyclyl), -(C_1-C_6 alkyl)-(5- to 10- membered heteroaryl), -(C_1-C_6 alkyl)-(5- to 10- membered heterocyclyl) or, together with R_3 represents a C_2-C_4 alkylene group;
- n is 0, 1, 2, 3 or 4;
- X represents a -CH_2-, -CO-, -SO- or -$S(O)_2$- group; and
- Het represents a 5- membered heteroaryl group or a 5- membered heterocyclyl group;

wherein:

- the alkyl and alkylene groups and moieties in the substituents R_1 to R_4 are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same

or different and are selected from halogen, hydroxy, amino, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylamino and di(C_1-C_4 alkyl)amino substituents; and

the aryl, heteroaryl, heterocyclyl and carbocyclyl groups and moieties in the substituents R_1, R_4 and Het are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, hydroxy, nitro, cyano, amino, C_1-C_6 alkylamino, di-(C_1-C_6 alkyl)amino, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy and C_1-C_6 haloalkylthio substituents.

2. Use according to claim 1 wherein the alkyl and alkylene groups and moieties in the substituents R_1 to R_4 are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_2 alkoxy, C_1-C_2 alkylthio, C_1-C_2 alkylamino and di(C_1-C_2 alkyl) amino substituents.

3. Use according to claim 2, wherein the alkyl and alkylene groups and moieties in the substituents R_1 to R_4 are unsubstituted or are substituted by one or two substituents selected from hydroxy, C_1-C_2 alkoxy and C_1-C_2 alkylthio substituents.

4. Use according to any one of the preceding claims, wherein, when an aryl, heteroaryl, heterocyclyl or carbocyclyl group or moiety in the substituent R_1, R_4 or Het carries a nitro or cyano substituent, only one of the substituents on the aryl, heteroaryl, heterocyclyl or carbocyclyl group is a nitro or cyano group.

5. Use according to any one of the preceding claims, wherein the aryl, heteroaryl, heterocyclyl and carbocyclyl groups and moieties in the substituents R_1, R_4 and Het are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_1-C_4 alkylthio, hydroxy, cyano, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy and C_1-C_4 haloalkylthio substituents.

6. Use according to claim 5, wherein the aryl, heteroaryl, heterocyclyl and carbocyclyl groups and moieties in the substituents R_1, R_4 and Het are unsubstituted

or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, hydroxy, cyano, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy and C_1-C_2 haloalkylthio substituents.

7. Use according to any one of the preceding claims, wherein R_1 is hydrogen, C_1-C_6 alkyl, C_6-C_{10} aryl, a 5- to 10- membered heteroaryl group or a C_3-C_6 cycloalkyl group.

8. Use according to claim 7 wherein, when R_1 is C_1-C_6 alkyl or C_3-C_6 cycloalkyl, it is unsubstituted.

9. Use according to any one of the preceding claims, wherein, when n is more than 1, not more than one R_2 substituent represents a group selected from nitro and cyano.

10. Use according to any one of the preceding claims, wherein each R_2 is the same or different and represents C_1-C_4 alkyl, halogen, C_1-C_4 alkoxy, C_1-C_4 alkylthio, hydroxy, nitro, cyano, amino, (C_1-C_4 alkyl)amino or di(C_1-C_4 alkyl)amino.

11. Use according to any one of the preceding claims, wherein the or each R_2 substituent is unsubstituted.

12. Use according to any one of the preceding claims, wherein n is 0, 1 or 2.

13. Use according to any one of the preceding claims, wherein X_2 represents $-CH_2-$.

14. Use according to any one of the preceding claims, wherein R_3 represents hydrogen or C_1-C_4 alkyl or, together with R_4, represents an unsubstituted C_2-C_4 alkylene group.

15. Use according to any one of the preceding claims, wherein the R_3 substituent is unsubstituted and, when R_3 and R_4 together represent a C_2-C_4 alkylene group, the

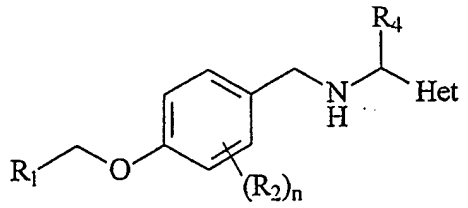
C_2-C_4 alkylene group is unsubstituted.

16. Use according to any one of the preceding claims, wherein R_4 represents hydrogen, C_1-C_6 alkyl, C_6-C_{10} aryl, C_3-C_6 carbocyclyl, a 5- to 10- membered heteroaryl group, a 5- to 10- membered heterocyclyl group, -(C_1-C_2 alkyl)-(C_6-C_{10} aryl), -(C_1-C_2 alkyl)-(C_3-C_6 carbocyclyl), -(C_1-C_2 alkyl)-(5- to 10- membered heteroaryl), -(C_1-C_2 alkyl)-(5- to 10- membered heterocyclyl) or, together with R_3, represents a C_2-C_4 alkylene group.

17. Use according to claim 16 wherein R_4 represents hydrogen, C_1-C_4 alkyl, phenyl, C_3-C_6 cycloalkyl, a 5- or 6- membered heteroaryl group, -(C_1-C_2 alkyl)-phenyl or, together with R_3, represents an unsubstituted C_2-C_4 alkylene group.

18. Use according to any one of the preceding claims, wherein Het is a 5-membered heteroaryl group containing 1 or 2 heteroatoms selected from N, O and S.

19. Use according to any one of the preceding claims, wherein the compound of formula (II) is a compound of formula (IIa),



(IIa)

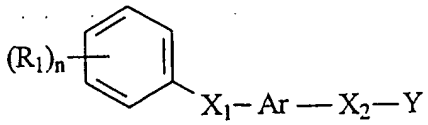
wherein:

- R_1 is hydrogen, an unsubstituted C_1-C_4 alkyl group, an unsubstituted cyclohexyl group or a phenyl group which is unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, cyano, C_1-C_2 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy and C_1-C_2 haloalkylthio substituents;
- each R_2 is the same or different and represents halogen, hydroxyl, amino, nitro or an unsubstituted C_1-C_2 alkyl, C_1-C_2 alkoxy, (C_1-C_2 alkyl)amino or

di(C_1-C_2 alkyl)amino group, provided that not more than one R_2 substituent is nitro;

- R_4 represents hydrogen or an unsubstituted C_1-C_4 alkyl, phenyl or benzyl group;
- Het is a 5- membered heteroaryl group containing 1 or 2 heteroatoms selected from N, O and S, which is unsubstituted or substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_2 alkyl and C_1-C_2 haloalkyl substituents; and
- n is 0, 1 or 2.

20. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment or prevention of a condition where SNS sodium channels are involved in the underlying mechanism of the disease or in producing symptoms that can be treated separately



(I)

wherein:

- each R_1 is the same or different and represents halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, hydroxy, amino, C_1-C_6 alkylamino or di-(C_1-C_6 alkyl)amino;
- n is 0, 1, 2 or 3;
- X_1 represents a direct bond, -L-O-L$'$-, -L-S-L$'$- or -L-NR$'$-L$'$- wherein L and L$'$ are the same or different and each represent a direct bond or C_1-C_4 alkylene group and R$'$ represents hydrogen or C_1-C_4 alkyl;
- Ar represents a 5- to 6- membered heteroaryl group or a phenyl group which is optionally fused to a 5- membered heteroaryl group;
- X_2 represents a direct bond, -L$''$-O-, -L$''$-S-, L$''$-NR$'$-, -CO-, -CO_2-, -S(O)-, -$S(O)_2$-, -CO-NR$'$-, -S(O)-NR$'$- or -$S(O)_2$-NR$'$-, wherein L$''$ represents a direct bond or C_1-C_4 alkylene group and R$'$ represents hydrogen or C_1-C_4 alkyl; and

- Y represents $-L'''-NR'R''$ or a $-(C_1-C_6$ alkyl)-(5- to 10- membered heteroaryl), $-(C_1-C_6$ alkyl)-(5- to 10- membered heterocyclyl), $-(C_1-C_6$ alkyl)-phenyl, phenyl, 5- to 10- membered heteroaryl or 5- to 10- membered heterocyclyl group, wherein L''' is a C_1-C_4 alkylene group and R' and R'' are the same or different and each represent hydrogen, C_1-C_6 alkyl or phenyl, provided that (a) when Y is a 5- to 10- membered heteroaryl group it is other than a pyridyl group and (b) when X_1 is -O-, -S- or $-NR'-$, X_2 is a direct bond and Y is a 5- to 10- membered heteroaryl group which contains 1 or 2 heteroatoms selected from N, O and S, the 5- to 10- membered heteroaryl group is attached via a carbon atom which is not adjacent to a N atom,

wherein:

- the alkyl and alkylene groups and moieties in the substituents R_1, X_1, X_2 and Y are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylamino and di(C_1-C_4 alkyl)amino substituents; and
- the phenyl, heteroaryl and heterocyclyl groups in the substituents Ar_1 and Y are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, hydroxy, $-NR'R''$, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 haloalkylthio, cyano, nitro, $-CONR'R''$, $-S(O)_2-NR'R''$, $-CO_2-R''$, $-S(O)_2R''$ and phenyl substituents, wherein R' and R'' are the same or different and each represent hydrogen or C_1-C_4 alkyl.

21. Use according to claim 20, wherein the alkyl and alkylene groups and moieties in the substituents R_1, X_1, X_2 and Y are unsubstituted or are substituted by 1 or 2 substituents selected from halogen, hydroxy, C_1-C_2 alkoxy and C_1-C_2 alkylthio substituents.

22. Use according to claim 20 or 21, wherein the phenyl, heteroaryl and heterocyclyl groups and moieties in the substituents Ar and Y are unsubstituted or are substituted by 1 or 2 substituents which are the same or different and are selected

from halogen, hydroxy, amino, C_1-C_2 alkyl, C_1-C_2 alkoxy, C_1-C_2 alkylthio, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_2 haloalkylthio, carbamyl and phenyl substituents.

23. Use according to any one of claims 20 to 22, wherein each R_1 is the same or different and represents halogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or C_1-C_4 alkylthio.

24. Use according to claim 23, wherein each R_1 is the same or different and represents halogen or an unsubstituted C_1-C_2 alkyl, C_1-C_2 haloalkyl, C_1-C_2 alkoxy, C_1-C_2 haloalkoxy, C_1-C_2 alkylthio or C_1-C_2 haloalkylthio group.

25. Use according to any one of claims 20 to 24, wherein n is 0, 1 or 2.

26. Use according to any one of claims 20 to 25, wherein each L and L′ moiety in the X_1 group is a direct bond or a methylene or ethylene group.

27. Use according to any one of claims 20 to 26, wherein X_1 is -O- or -S-.

28. Use according to any one of claims 20 to 26, wherein X_1 is -L-O- or -L-S- wherein L is a C_1-C_4 alkylene group.

29. Use according to any one of claims 20 to 26, wherein X_1 is a direct bond.

30. Use according to any one of claims 20 to 29, wherein Ar is a 5- membered heteroaryl group, a phenyl group or a phenyl group fused to a 5- membered heteroaryl group.

31. Use according to any one of claims 20 to 30, wherein the Ar group is unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, hydroxy, C_1-C_2 alkyl, C_1-C_2 haloalkyl, C_1-C_2 alkoxy, C_1-C_2 haloalkoxy, C_1-C_2 alkylthio and C_1-C_2 haloalkylthio substituents.

32. Use according to any one of claims 20 to 31, wherein each L″ moiety in the X_2 group is a methylene or ethylene group.

33. Use according to any one of claims 20 to 32, wherein X_2 represents a direct bond, -L''-NR'-, -CO-, -S(O)-, -$S(O)_2$-, -CO-NR'- or -$S(O)_2$-NR'- wherein L'' is as defined in any one of the preceding claims and R' is hydrogen, methyl or ethyl.

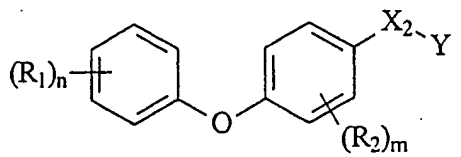
34. Use according to any one of claims 20 to 33, wherein X_2 is not a direct bond when X_1 is -O-, -S-, -NR'- or a direct bond.

35. Use according to any one of claims 20 to 34, wherein L''' in the Y substituent is an unsubstituted C_1-C_4 alkylene group.

36. Use according to any one of claims 20 to 35, wherein Y represents -(C_1-C_4 alkyl)-N(C_1-C_4 alkyl)$_2$, or a -(C_1-C_4 alkyl)-(5- to 10- membered heteroaryl), -(C_1-C_4 alkyl)-(5- to 10- membered heterocyclyl), -(C_1-C_4 alkyl)-phenyl, phenyl, 5-membered heteroaryl or 5- to 10- membered heterocyclyl group, provided that when X_1 is -O-, -S- or -NR'-, X_2 is a direct bond and Y is a heteroaryl group which contains 1 or 2 heteroatoms selected from N, O or S, Y is attached via a carbon atom which is not adjacent to a N atom.

37. Use according to any one of claims 20 to 36, wherein whenever Y is a 5-membered heteroaryl group, either X_1 is -O-CH_2- or X_2 is other than a direct bond.

38. Use according to any one of claims 20 to 37, wherein the compound of formula (I) is a compound of formula (Ia)



(Ia)

wherein:

- each R_1 is the same or different and is as defined in any one of claims 20 to 37;
- n is as defined in any one of claims 20 to 37;

- each R_2 is the same or different and is halogen, hydroxy, C_1-C_2 alkyl, C_1-C_2 haloalkyl, C_1-C_2 alkoxy, C_1-C_2 haloalkoxy, C_1-C_2 alkylthio or C_1-C_2 haloalkylthio;
- m is 0, 1 or 2;
- X_2 is as defined in any one of claims 20 to 37; and
- Y is -(C_1-C_4 alkyl)-N(C_1-C_4 alkyl)$_2$ or a -(C_1-C_4 alkyl)-(5- to 6- membered heteroaryl), -(C_1-C_4 alkyl)-(5- to 10- membered heterocyclyl), 5- membered heteroaryl or 5- to 10- membered heterocyclyl group, provided that when X_2 is a direct bond and Y is a heteroaryl group containing 1 or 2 heteroatoms selected from N, O and S, Y is attached via a carbon atom which is not adjacent to a nitrogen atom,

wherein:

- the alkyl and alkylene groups and moieties in the substituents R_1, R_2, X_2 and Y are unsubstituted; and
- the heteroaryl and heterocyclyl groups and moieties in the substituent Y are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_2 alkyl, C_1-C_2 alkoxy, C_1-C_2 alkylthio, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_2 haloalkylthio, carbamyl and phenyl substituents.

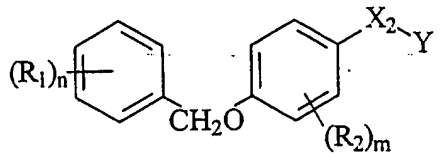
39. Use according to claim 38, wherein each R_1 in the formula (Ia) is the same or different and is a halogen atom, n in the formula (Ia) is 0, 1 or 2, and/or X_2 in the formula (Ia) is -CH_2-NH-, -$S(O)_2$-NH- or -$S(O)_2$-.

40. Use according to claim 38 or 39, wherein each R_2 in the formula (Ia) is the same or different and is C_1-C_2 alkyl or C_1-C_2 alkoxy, and/or m in the formula (Ia) is 0 or 1.

41. Use according to any one of claims 38 to 40, wherein Y in the formula (Ia) is -(C_1-C_2 alkyl)-N(C_1-C_2 alkyl)$_2$ or a -(C_1-C_2 alkyl)-(5- to 6- membered heteroaryl), -(C_1-C_2 alkyl)-(5- to 6- membered heterocyclyl), 5- membered heteroaryl or 5- to 6- membered heterocyclyl group, provided that when X_2 is a direct bond and Y is a

heteroaryl group containing 1 or 2 heteroatoms selected from N, O and S, Y is attached via a carbon atom which is not adjacent to a nitrogen atom.

42. Use according to any one of claims 20 to 37, wherein the compound of formula (I) is a compound of formula (Ib)



(Ib)

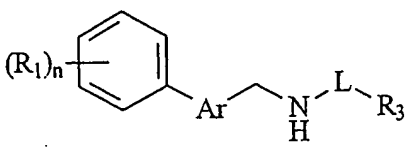
wherein:

- R_1, R_2, m and X_2 are as defined in any one of claims 38 to 41; and
- Y is -(C_1-C_4 alkyl)-N(C_1-C_4 alkyl)$_2$ or a -(C_1-C_4 alkyl)-(5- to 6- membered heteroaryl), -(C_1-C_4 alkyl)-(5- to 10- membered heterocyclyl), 5- membered heteroaryl or 5- to 10- membered heterocyclyl group,

wherein:

- the alkyl and alkylene groups and moieties in the substituents R_1, R_2, X_2 and Y are unsubstituted; and
- the heteroaryl and heterocyclyl groups and moieties in the substituent Y are unsubstituted or substituted by one or two substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_2 alkyl, C_1-C_2 alkoxy, C_1-C_2 alkylthio, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_2 haloalkylthio, carbamyl and phenyl substituents.

43. Use according to any one of claims 20 to 37, wherein the compound of formula (I) is a compound of formula (Ic)



(Ic)

wherein:

- each R_1 is the same or different and is as defined in any one of claims 20 to 42;

- n is as defined in any one of claims 20 to 42;
- Ar is as defined in any one of claims 20 to 42;
- L is a C_1-C_4 alkylene group; and
- R_3 is phenyl, 5- to 6- membered heteroaryl or 5- to 6- membered heterocyclyl,

wherein:

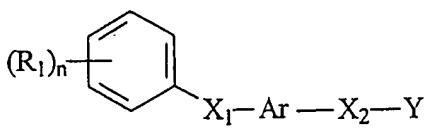
- the alkyl and alkylene groups and moieties in the substituents R_1 and L are unsubstituted; and
- the phenyl, heteroaryl and heterocyclyl groups and moieties in the substituents Ar and R_3 are unsubstituted or are substituted by one or two substituents selected from halogen, C_1-C_2 alkyl, C_1-C_2 alkoxy, C_1-C_2 alkylthio, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy and C_1-C_2 haloalkylthio substituents.

44. Use according to claim 43, wherein Ar in the formula (Ic) is an unsubstituted triazolyl, imidazolyl, phenyl, benzofuranyl, benzothienyl or indolyl group.

45. Use according to claim 43 or 44, wherein R_3 in the formula (Ic) is a phenyl or 5- membered heteroaryl group which is unsubstituted or substituted by a C_1-C_2 alkyl substituent.

46. Use according to any one of the preceding claims, wherein said medicament is for use in the treatment or prevention of a condition selected from chronic and acute pain, tinnitus, bowel disorders, bladder dysfunction and demyelinating diseases.

47. A compound of formula (I'), or a pharmaceutically acceptable salt thereof, for use in the treatment of the human or animal body,



(I')

wherein:

- each R_1 is the same or different and represents halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, hydroxy, amino, C_1-C_6 alkylamino or di-(C_1-C_6 alkyl)amino;
- n is 0, 1, 2 or 3;
- X_1 represents a direct bond, -L-O-L'-, -L-S-L'- or -L-NR'-L'- wherein L and L' are the same or different and each represent a direct bond or C_1-C_4 alkylene group and R' represents hydrogen or C_1-C_4 alkyl;
- Ar represents a 5- to 6- membered heteroaryl group or a phenyl group which is optionally fused to a 5- membered heteroaryl group;
- X_2 represents a direct bond, -L''-O-, -L''-S-, L''-NR'-, -CO-, -CO_2-, -S(O)-, -$S(O)_2$-, -CO-NR'-, -S(O)-NR'- or -$S(O)_2$-NR'-, wherein L'' represents a direct bond or C_1-C_4 alkylene group and R' represents hydrogen or C_1-C_4 alkyl; and
- Y represents -L'''-NR'R'' or a -(C_1-C_6 alkyl)-(5- to 10- membered heteroaryl), -(C_1-C_6 alkyl)-(5- to 10- membered heterocyclyl), -(C_1-C_6 alkyl)-phenyl, phenyl, 5- to 10- membered heteroaryl or 5- to 10- membered heterocyclyl group, wherein L''' is a C_1-C_4 alkylene group and R' and R'' are the same or different and each represent hydrogen, C_1-C_6 alkyl or phenyl, provided that (a) when Y is a 5- to 10- membered heteroaryl group it is other than a pyridyl group and (b) when X_1 is -O-, -S- or -NR'-, X_2 is a direct bond and Y is a 5- to 10- membered heteroaryl group which contains 1 or 2 heteroatoms selected from N, O and S, the 5- to 10- membered heteroaryl group is attached via a carbon atom which is not adjacent to a N atom,

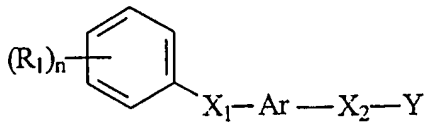
wherein:

- the alkyl and alkylene groups and moieties in the substituents R_1, X_1, X_2 and Y are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylamino and di(C_1-C_4 alkyl)amino substituents; and
- the phenyl, heteroaryl and heterocyclyl groups in the substituents Ar_1 and Y are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy,

C_1-C_6 alkylthio, hydroxy, -$NR'R''$, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 haloalkylthio, cyano, -$CONR'R''$, -$S(O)_2$-$NR'R''$, -CO_2-R'', -$S(O)_2R''$ and phenyl substituents, wherein R' and R'' are the same or different and each represent hydrogen or C_1-C_4 alkyl,

provided that the compound of formula (I') is other than 4-[4-(benzyloxy)phenyl]-1H-pyrazole.

48. A compound of formula (II") or a pharmaceutically acceptable salt thereof



(I")

wherein:

- each R_1 is the same or different and represents halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, hydroxy, C_1-C_6 alkylamino or di-(C_1-C_6 alkyl)amino;
- n is 0, 1, 2 or 3;
- X_1 represents a direct bond, -L-O-L'-, -L-S-L'- or -L-NR'-L'- wherein L and L' are the same or different and each represent a direct bond or C_1-C_4 alkylene group and R' represents hydrogen or C_1-C_4 alkyl;
- Ar represents a 5- to 6- membered heteroaryl group or a phenyl group which is optionally fused to a 5- membered heteroaryl group;
- X_2 represents a direct bond, -L''-O-, -L''-S-, L''-NR'-, -CO-, -CO_2-, -S(O)-, -$S(O)_2$-, -CO-NR'-, -S(O)-NR'- or -$S(O)_2$-NR'-, wherein L'' represents a direct bond or C_1-C_4 alkylene group and R' represents hydrogen or C_1-C_4 alkyl; and
- Y represents -L'''-$NR'R''$ or a -(C_1-C_6 alkyl)-(5- to 10- membered heteroaryl), -(C_1-C_6 alkyl)-(5- to 10- membered heterocyclyl), -(C_1-C_6 alkyl)-phenyl, phenyl, 5- to 10- membered heteroaryl or 5- to 10- membered heterocyclyl group, wherein L''' is a C_1-C_4 alkylene group and R' and R'' are the same or different and each represent hydrogen, C_1-C_6 alkyl or phenyl, provided that (a) when Y is a 5- to 10- membered heteroaryl group it is other than a pyridyl group and (b) when X_1 is -O-, -S- or -NR'-, X_2 is a direct bond and Y is a 5- to 10- membered heteroaryl group which contains 1 or 2 heteroatoms selected

from N, O and S, the 5- to 10- membered heteroaryl group is attached via a carbon atom which is not adjacent to a N atom,

wherein:

- the alkyl and alkylene groups and moieties in the substituents R_1, X_1, X_2 and Y are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, hydroxy, amino, C_1-C_4 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylamino and di(C_1-C_4 alkyl)amino substituents; and
- the phenyl, heteroaryl and heterocyclyl groups in the substituents Ar_1 and Y are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 alkylthio, hydroxy, -$NR'R''$, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxy, C_1-C_6 haloalkylthio, cyano, -$CONR'R''$, -$S(O)_2$-$NR'R''$, -CO_2-R'', -$S(O)_2R''$ and phenyl substituents, wherein R' and R'' are the same or different and each represent hydrogen or C_1-C_4 alkyl.

provided that the compound of formula (I") is other than 4-[4-(benzyloxy)phenyl]-1H-pyrazole.

49. A compound according to claim 47 or 48, wherein R_1, n, X_1, Ar, X_2 and Y are as defined in any one of claims 20 to 45.

50. A compound of the formula (II), as defined in any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, for use in the treatment of the human or animal body.

51. A pharmaceutical composition comprising a compound according to any one of claims 47 to 50 and a pharmaceutically acceptable carrier or diluent.

52. A composition according to claim 51 which is a capsule or tablet comprising from 10 to 500 mg of the compound according to any one of claims 47 to 50.

53. An inhalation device comprising a pharmaceutical composition according to claim 51.

54. An inhalation device according to claim 53, which is a nebulizer.

55. A compound of the formula (II) as defined in any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof, in which Het is other than furanyl.

56. A method of treating a patient suffering from or susceptible to a condition defined in claim 1 or 46, which method comprises administering to said patient an effective amount of a compound of formula (I), as defined in any one of claims 20 to 45, a compound of formula (II), as defined in any one of claims 1 to 19, or a pharmaceutically acceptable salt thereof.

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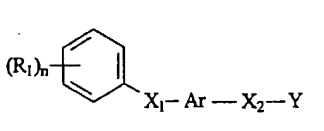
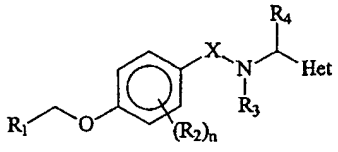


(I)



(II)

(57) Abstract: Compounds of the formulae (I) and (II), and pharmaceutically acceptable salts thereof, are found to be inhibitors of sensory neurone specific (SNS) sodium channels. They are therefore useful as analgesic and neuroprotective agents. Formula (I) & Formula (II) wherein, in the formula (I), R_1 is an organic substituent, X_1 and X_2 are direct bonds or spacer moieties, Ar is aryl or heteroaryl and Y is a substituted aminoalkyl group or a heteroaryl-, heterocyclyl- or phenyl-containing moiety and, in the formula(II), R_1, R_2, R_3, Ar and R_4 are organic substituents, X is a spacer moiety and Het is a 5-membered heteroaryl or heterocyclyl group.

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INTERNATIONAL SEARCH REPORT

PCT/GB2004/002697

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4439

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/069275 A1 (DEVASTHALE PRATIK ET AL) 10 April 2003 (2003-04-10) page 12, paragraph 27	1-56
X	WO 01/21602 A (DEVASTHALE PRATIK ; SQUIBB BRISTOL MYERS CO (US); CHEN SEAN (US); JEON) 29 March 2001 (2001-03-29) page 16, lines 3-15	1-56
P,X	WO 2004/024715 A (BURROWS JEREMY NICHOLAS ; TUCKER HOWARD (GB); ASTRAZENECA UK LTD (GB);) 25 March 2004 (2004-03-25) page 1, lines 3-5 page 2, lines 1-11	1-56

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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